

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND COUNTER-
DESIGNATIONS FOR MARILYN J. COLLICOTT**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition designations and counter-designations for the September 27, 2006 deposition of Marilyn J. Collicott Clinical Project Manager, ABT-594 Team, Abbott Laboratories.

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: /s/ Eric J. Lorenzini
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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008

/s/ Ozge Guzelsu

Marilyn Collicott Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/27/06	Collicott, Marilyn	5:7-6:8	8:10-8:13	6:14-7:8 7:19-8:6	1		1
09/27/06	Collicott, Marilyn	8:14-9:20		10:3-10:7 10:11-10:17			
09/27/06	Collicott, Marilyn	11:19-12:19					
09/27/06	Collicott, Marilyn	14:5-14:24					
09/27/06	Collicott, Marilyn	15:2-15:20	15:21-16:3 16:14-17:1				
09/27/06	Collicott, Marilyn	21:7-22:18		18:14-19:10			
09/27/06	Collicott, Marilyn	24:4-24:9	23:4-23:9				
09/27/06	Collicott, Marilyn	25:10-26:7	25:1-25:8				
09/27/06	Collicott, Marilyn	27:11-28:10	26:8-26:19 28:17-29:7				
09/27/06	Collicott, Marilyn	29:9-30:7	30:10-30:15				
09/27/06	Collicott, Marilyn	31:5-31:10		31:12-31:19			
09/27/06	Collicott, Marilyn	32:22-33:24		45:12-48:5			
09/27/06	Collicott, Marilyn	49:20-50:7		50:9-52:17			
09/27/06	Collicott, Marilyn	52:18-54:8					
09/27/06	Collicott, Marilyn	56:1-56:11					
09/27/06	Collicott, Marilyn	57:2-57:16					

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/27/06	Collicott, Marilyn	61:21-63:11					
09/27/06	Collicott, Marilyn	65:9-65:20	65:22-66:1				
09/27/06	Collicott, Marilyn	66:17-67:13	67:14-68:13				
09/27/06	Collicott, Marilyn	68:15-69:14		69:15-70:21			
09/27/06	Collicott, Marilyn	71:21-72:10	72:11-73:3				
09/27/06	Collicott, Marilyn	78:8-79:1					
09/27/06	Collicott, Marilyn	79:20-80:5					
09/27/06	Collicott, Marilyn	80:24-81:3			2	BV	
09/27/06	Collicott, Marilyn	82:21-84:10	84:17-85:12		2	BV	
09/27/06	Collicott, Marilyn			88:10-88:15	4		GK
09/27/06	Collicott, Marilyn			89:9-89:13	4		
09/27/06	Collicott, Marilyn			90:7-90:12			
09/27/06	Collicott, Marilyn			98:13-99:8			
09/27/06	Collicott, Marilyn			99:17-100:8			
09/27/06	Collicott, Marilyn			100:20-101:10			
09/27/06	Collicott, Marilyn	103:12-104:1	104:2-104:9		2	BV	
09/27/06	Collicott, Marilyn	105:13-107:14	107:16-108:4 109:4-109:21		7	CE	
09/27/06	Collicott, Marilyn	109:24-110:11			7	CE	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/27/06	Collicott, Marilyn	112:10-113:1	113:2-113:3		7	CE	
09/27/06	Collicott, Marilyn	115:1-116:18	114:19-114:24 119:6-119:8		8	HQ	
09/27/06	Collicott, Marilyn	133:19-134:7			11	CR	
09/27/06	Collicott, Marilyn	135:2-137:13			11	CR	
09/27/06	Collicott, Marilyn	145:11-145:16			15	DB	
09/27/06	Collicott, Marilyn	146:15-148:19			16	DD	
09/27/06	Collicott, Marilyn			151:7-153:9	16	DD	
09/27/06	Collicott, Marilyn			154:1-154:10			
09/27/06	Collicott, Marilyn			156:19-157:7			
09/27/06	Collicott, Marilyn			157:16-158:17	18		GL
09/27/06	Collicott, Marilyn	172:8-173:6			22	DU	
09/27/06	Collicott, Marilyn	173:13-174:2			22	DU	
09/27/06	Collicott, Marilyn	176:11-177:17			23	IH	
09/27/06	Collicott, Marilyn	176:11-177:17			23	IH	
09/27/06	Collicott, Marilyn	179:17-179:22			24	DV	
09/27/06	Collicott, Marilyn	180:16-180:23			24	DV	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/27/06	Collicott, Marilyn	182:12-185:9		186:5-187:20 188:8-189:3 190:19-191:7	25	DX	
09/27/06	Collicott, Marilyn	193:6-193:17			26	20	
09/27/06	Collicott, Marilyn	195:6-196:22			27	ED	
09/27/06	Collicott, Marilyn			200:3-202:14	28		LI
09/27/06	Collicott, Marilyn	202:15-203:6		203:7-203:16 205:14-206:7 206:14-207:20	29 30	SK	GM
09/27/06	Collicott, Marilyn	208:16-209:1			31	EK	
09/27/06	Collicott, Marilyn	209:14-209:18			31	EK	
09/27/06	Collicott, Marilyn	209:24-210:24			31	EK	
09/27/06	Collicott, Marilyn	212:19-213:15	214:11-214:19		32	EL	
09/27/06	Collicott, Marilyn	214:20-215:12			32	EL	
09/27/06	Collicott, Marilyn	216:22-218:11			29	SK	
09/27/06	Collicott, Marilyn			231:1-231:7			
09/27/06	Collicott, Marilyn			236:12-236:15			
09/27/06	Collicott, Marilyn			243:10-243:16			

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/27/06	Collicott, Marilyn	243:17-244:10	244:20-244:22 245:2-245:9		38	FK	
09/27/06	Collicott, Marilyn			248:3-250:19	39		GN
09/27/06	Collicott, Marilyn	255:4-257:19			42	FV	
09/27/06	Collicott, Marilyn		258:14-259:18				
09/27/06	Collicott, Marilyn	261:3-261:6					
09/27/06	Collicott, Marilyn	266:6-266:11			45	GH	
09/27/06	Collicott, Marilyn	269:1-270:24	271:1-271:4	275:2-275:10	45	GH	

Color Key to Deposition Designations

 **Designation by Plaintiffs**

 **Counter Designation by Defendants**

 **Designation by Defendants**

Collicott, Marilyn J. (Linked) 9/27/2006 9:16:00 AM

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS

3
4 JOHN HANCOCK LIFE INSURANCE)
5 COMPANY, JOHN HANCOCK VARIABLE)
6 LIFE INSURANCE COMPANY and)
7 MANULIFE INSURANCE COMPANY)
8 (f/k/a/ INVESTORS PARTNER)
9 INSURANCE COMPANY),)

10 Plaintiffs,) Civil Action No.
11 -vs-) 05-11150-DPW

12 ABBOTT LABORATORIES,)
13 Defendant.)

14

15

16 THE DEPOSITION OF
17 MARILYN J. COLLICOTT

18

19 September 27, 2006

20

21

22

23

24

1 sworn.)

2 MARILYN J. COLLICOTT,

3 called as a witness herein, having been first duly

4 sworn, was examined and testified as follows:

5 EXAMINATION

6 BY MR. DAVIS:

7 Q. Good morning.

8 A. Good morning.

9 Q. Would you state your name, please, for
10 the transcript.

11 A. Marilyn J. Collicott.

12 Q. Where do you live, Mr. Collicott?

13 A. I live in Hales Corners, Wisconsin.

14 Q. What is the street address?

15 A. 6220 South 121st.

16 Q. Are you currently employed?

17 A. Yes.

18 Q. Where?

19 A. Abbott Laboratories.

20 Q. How long have you worked for Abbott?

21 A. Almost 14 years.

22 Q. What is your current position at Abbott?

23 A. Clinical project manager.

24 Q. How long have you held that position?

1 A. Since about 1998.

2 Q. Your position is clinical project

3 manager?

4 A. Project manager.

5 Q. Is it fair to say that you held that

6 position since 1998 but you worked on various

7 clinical trials since 1998?

8 A. Yes.

9 MR. DAVIS: We will mark this as the first

10 exhibit, if we may.

11 We are going to mark exhibits by witness

12 starting with 1. If we try to do sequentially in

13 this case, it will become a nightmare.

14 (WHEREUPON, a certain document was

15 marked Collicott Deposition Exhibit

16 No. 1, for identification, as of

17 09-27-2006.)

18 BY MR. DAVIS:

19 Q. Ms. Collicott, you have what has been

20 marked as Exhibit 1. Would you take a minute, look

21 at that and let me know if that is a copy of your

22 resume at least as of the middle of 2000.

23 A. Yes.

24 Q. In this resume -- does this date from

1 May of 2000?

2 MR. PHILLIPS: "This" being the resume itself.

3 MR. DAVIS: The resume itself.

4 BY THE WITNESS:

5 A. I believe it was.

6 BY MR. DAVIS:

7 Q. Was it accurate at that point in time?

8 A. Um-hmm.

9 MR. PHILLIPS: I'm sorry. You need to respond

10 verbally. In other words, yes, no.

11 THE WITNESS: Sorry.

12 MR. PHILLIPS: Whatever else your verbal

13 response is.

14 THE WITNESS: No uh-uhs.

15 BY MR. DAVIS:

16 Q. Actually we will both talk to you about

17 that if the need arises because I can't use the

18 um-hmms either.

19 So, this was accurate as of

20 approximately May of 2000.

21 You noted earlier that your position is

22 clinical project manager. I note that on this

23 resume that is the last position that you held. Is

24 it the same position that you hold today?

1 A. Yes.

2 Q. Have your duties or responsibilities

3 changed in any significant way since 2000?

4 MR. PHILLIPS: Objection.

5 BY THE WITNESS:

6 A. Other than trials that I'm working on.

7 BY MR. DAVIS:

8 Q. Well, as a -- let's take a step back for

9 a moment.

10 What do you do as a clinical project

11 manager?

12 A. I manage clinical trials everywhere from

13 start-up to closeout and any phase, I through IV.

14 Q. Have your duties as a clinical project

15 manager changed in any significant way since --

16 A. No.

17 Q. -- since, say, 2000?

18 The only other thing I will ask, please

19 let me finish my question so that we will get a

20 clean transcript and our reporter will not pull her

21 hair out.

22 Now, you have the dubious benefit of

23 being one of the first people deposed in this case,

24 which means that you get the pleasure of helping us

1 to define all of the terms that we will be using in
2 this case. So, excuse me. Some of these things
3 may seem obvious to you, but it's important that we
4 establish them for the record.

5 So, you mentioned a moment ago clinical
6 trials. What is a clinical trial?

7 A. It is a human trial on drugs that have
8 not been approved yet by the Federal Government.

9 Q. Approximately how many clinical trials
10 have you overseen?

11 MR. PHILLIPS: Objection; vague. I'm sorry.
12 Objection.

13 BY THE WITNESS:

14 A. 15.

15 BY MR. DAVIS:

16 Q. By "overseen" I meant managed. Is it
17 the same number?

18 A. I would say 15, yes.

19 Q. How many of those have been with Abbott?

20 A. All of them.

21 Q. Now, looking back again at your resume
22 for a moment, before you worked with Abbott, you
23 worked with a company named Surgitek, is that
24 right?

1 A. Correct.

2 Q. What did you do at Surgitek?

3 A. My last position was acting quality

4 assurance/quality control manager.

5 Q. Is it true that you moved from Surgitek

6 to Abbott in approximately 1993?

7 A. Correct.

8 Q. Why did you leave Surgitek?

9 A. Surgitek was being sold by Bristol-Myers

10 to another company and they were downsizing.

11 Q. When you began to work for Abbott your

12 first position was clinical research associate?

13 A. Correct.

14 Q. Did you oversee clinical trials in that

15 capacity?

16 A. I assisted with clinical trials. I did

17 not manage them.

18 Q. Was that your first exposure to clinical

19 trials?

20 A. I was exposed to clinical trials from a

21 quality perspective at Surgitek, but not

22 pharmaceutical trials.

23 Q. What responsibility did you have for

24 clinical trials while you were at Surgitek?

1 A. I was aware that they were going on. I
2 was doing testing in the lab to support regulatory
3 claims. But I did no conducting of any clinical
4 trials.

5 Q. So, at Surgitek, for example, you did
6 not -- you did not in fact run any clinical trials?

7 A. Correct.

8 Q. And as a clinical research associate at
9 Abbott, did you run clinical trials?

10 A. Not run them. I assisted running them.
11 I assisted the manager.

12 Q. And what duties did you have in
13 assisting the manager?

14 A. In most cases I was monitoring the
15 clinical trials. I would have been tracking
16 regulatory documents. I would have been writing
17 trip reports and assisting with the writing of
18 protocols, resolution of queries.

19 Q. When is the first time that you actually
20 oversaw or had primary responsibility for running a
21 clinical trial?

22 MR. PHILLIPS: I'm sorry. Could you read the
23 question.

24 (WHEREUPON, the record was read

1 by the reporter as requested as

2 follows: Q. When is the first

3 time that you actually oversaw or

4 had primary responsibility for

5 running a clinical trial?)

6 BY THE WITNESS:

7 A. To the best of my knowledge, I would say

8 that was probably about 1998, 1997.

9 BY MR. DAVIS:

10 Q. There are different phases of clinical

11 trials, is that correct?

12 A. That's correct.

13 Q. Have you managed or overseen Phase I

14 clinical trials?

15 A. Yes.

16 Q. Phase II clinical trials?

17 A. Yes.

18 Q. Phase III clinical trials?

19 A. Yes.

20 Q. Even within the various phases, there

21 are subphases, is that right?

22 A. Phase IIb, yes.

23 Q. What is the difference between, say, a

24 Phase IIa and a Phase IIb trial?

1 Q. The CV that we have already marked as
2 Exhibit 1, this accurately describes your
3 educational background?

4 A. Correct.

5 Q. You have a B.A. in chemistry and
6 biology?

7 A. Correct.

8 Q. Do you have any additional education,
9 formal education, beyond the B.A.?

10 A. No.

11 Q. Have you attended any other training
12 courses or graduate programs even if you haven't
13 obtained a degree?

14 A. No.

15 Q. How did you get your training to
16 operate, run clinical trials?

17 A. I was mentored and as you start as a
18 clinical research associate, you learn the ropes.
19 You become a senior research associate where you
20 get more responsibility and then a clinical project
21 manager. So, it's growing into the job.

22 Q. Was it training that you received at
23 Abbott?

24 A. Yes.

1 Q. Did you take any -- strike that.

2 Did Abbott provide you with any formal
3 courses or materials for purposes of training you
4 to run clinical trials?

5 A. Yes.

6 Q. What materials?

7 A. They would have been training courses
8 that I would have attended, not only at Abbott,
9 sponsored by Abbott, or have gone to conferences,
10 scientific meetings.

11 Q. You have on occasion taken training
12 courses that have been run by or sponsored by
13 Abbott?

14 A. Yes.

15 Q. Specific to operating clinical trials?

16 A. Yes.

17 Q. What's the last time you took a course
18 of that nature?

19 A. I would say probably within the last
20 year or two.

21 Q. What was that -- what did that course
22 entail?

23 A. Understanding GCPs.

24 Q. What are GCPs?

1 A. Good clinical practice.

2 Q. Who within Abbott gives the courses?

3 A. That would be our training department.

4 Q. Is there someone responsible that you're
5 aware of in charge of the training department?

6 A. I couldn't tell you the name.

7 Q. Do you know anyone who works within
8 Abbott's training department?

9 A. Sandra Cox.

10 Q. Do you know her title?

11 A. No.

12 Q. Does she work at Abbott Park?

13 A. Yes.

14 Q. Approximately how many Abbott training
15 courses have you taken?

16 A. Since?

17 Q. Since you started work at Abbott. Best
18 you recall.

19 A. I would say 20 to 30.

20 Q. Were all of those courses on having
21 something to do with clinical trials?

22 A. No.

23 Q. Approximately how many of them had
24 something to do with clinical trials?

1 A. I'd say about two-thirds.

2 Q. Have you yourself given -- ever given

3 any training courses on clinical trials?

4 A. I've mentored but I have not given

5 training courses.

6 Q. When you say you have mentored, what do

7 you mean?

8 A. I have mentored new hires, CRAs, people

9 that report to me.

10 Q. Who is your current superior, immediate

11 superior at Abbott?

12 A. Susan Glad Anderson.

13 Q. What is her position?

14 A. She is assistant director.

15 Q. Of?

16 A. Of -- I'm sorry. I believe it's

17 associate director. I get those mixed up. Just --

18 it's just the title associate director, like

19 clinical project manager.

20 Q. Take a step back for a second and talk

21 about the structure here. You are a clinical

22 project manager. Do you fall within some

23 department at Abbott?

24 A. Yes.

1 Q. What is the department?

2 A. Immunoscience.

3 Q. And so you are running clinical trials
4 on immunopharmaceuticals or compounds, is that
5 right?

6 A. Correct.

7 MR. PHILLIPS: Objection; vague. Well, I'm
8 just trying to make sure we are talking about --
9 what time period we are talking about.

10 MR. DAVIS: Currently.

11 BY THE WITNESS:

12 A. Currently, yes.

13 BY MR. DAVIS:

14 Q. Is there one -- within Abbott, is there
15 one overarching clinical trial division or
16 organization?

17 A. Global pharmaceutical research and
18 development.

19 Q. Within global pharmaceutical research
20 and development, are there different sort of
21 pillars or various subgroups that focus on
22 different aspects of healthcare?

23 A. Yes.

24 Q. For example, there is one on oncology,

1 is that right?

2 A. Correct.

3 Q. Another on immuno products, is that

4 right?

5 A. Immunoscience, correct.

6 Q. That is the one you currently work in?

7 A. Correct.

8 Q. What are the others?

9 A. Neuroscience, antiviral, renal. There

10 is probably some others.

11 Q. Have you worked with -- within -- what
12 are those called, by the way? Are they divisions?

13 A. Groups now. I believe they're called
14 just groups. Immunoscience group, neuroscience
15 group.

16 Q. Have you worked in other groups in the
17 past?

18 A. Yes.

19 Q. How many other groups have you worked
20 in?

21 A. Four -- five.

22 Q. Which ones?

23 A. When I first started, immunology, then
24 oncology, neuroscience. I did a bit of work in

1 Q. And depending on what programs are
2 available and what interests you, you make a
3 determination where you go, is that right?

4 A. I could choose to stay. There may be
5 other programs within my group I can move to. If
6 there is not, then I would find another group.

7 Q. At one point in time you worked on a
8 clinical trial involving a compound named ABT-594,
9 correct?

10 A. Yes.

11 Q. What group was that within?

12 A. At that time it was the analgesia
13 venture.

14 Q. What was the analgesia venture?

15 A. That was -- at one time Abbott was
16 divided into venture groups. That has since
17 changed. Now it would be the neuroscience group.
18 But at that time Abbott was doing a venture system.

19 Q. What is the difference between a venture
20 system and a group system, if you know?

21 A. Just the way it's organized.

22 Q. Was the analgesia venture disbanded by
23 Abbott at some point in time?

24 A. Yes.

1 Q. When?

2 A. I'm trying to think. Probably around --

3 let's look here when I went to oncology. Around

4 1999.

5 Q. Why?

6 A. The program was stopped.

7 Q. Did the program consist of more than one

8 compound?

9 A. I don't recall. I don't recall.

10 Q. Did you work on more than one clinical

11 trial involving ABT-594?

12 A. Yes.

13 Q. And if I refer in the course of the

14 deposition here today to 594, you understand I'm

15 referring --

16 A. Yes.

17 Q. -- to ABT-594?

18 A. Correct.

19 Q. How many clinical trials involving 594

20 did you work on?

21 A. Can you clarify if that's a trial that

22 actually got up and running or is it a trial that I

23 started?

24 Q. Any -- let's take a step back again.

1 The different clinical trials that you have worked
2 on within Abbott have trial numbers, is that right?

3 A. That's correct.

4 Q. What is the -- what's the numbering
5 system that Abbott uses for its clinical trials?
6 Can you describe it, please?

7 A. Certainly. It's an M number followed by
8 the year and then a sequential number that's given
9 out by central office.

10 Q. What does the M mean, if you know?

11 A. I don't know.

12 Q. All clinical trials within Abbott begin
13 with an M?

14 A. Most of them.

15 Q. So, if we had a trial that was M99, we
16 know that is a clinical trial that began in the
17 year '99?

18 A. It would have been the time that we
19 applied for the number. The trial may not have
20 actually started in '99. It could have been 2000.

21 Q. Then again it's followed by a --
22 typically a three-digit number?

23 A. Three-digit number.

24 Q. And those are just given out

1 sequentially within Abbott depending on which
2 trials start first?

3 A. When you apply for the number.

4 Q. How many trials with separate and
5 distinct trial numbers did you work on with respect
6 to 594?

7 A. Three.

8 Q. What trials were those?

9 A. M98-826, M99-114, M99-115.

10 Q. Now, what was the M98-826 trial? What
11 did that involve?

12 A. Osteoarthritis.

13 Q. Did that involve administering 594 to
14 subjects or patients to determine its effect on
15 their osteoarthritis?

16 MR. PHILLIPS: Objection.

17 BY THE WITNESS:

18 A. It would have been a safety and efficacy
19 trial for OA.

20 BY MR. DAVIS:

21 Q. What phase was it?

22 A. II I believe.

23 Q. Phase IIa or Phase IIb?

24 A. I just know it as a II.

1 Q. What is the difference between -- what
2 is a Phase I trial?

3 A. First time in man.

4 Q. Typically what are you looking for when
5 you run a Phase I trial?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. Safety.

9 BY MR. DAVIS:

10 Q. What is the -- the Phase II -- a
11 Phase II trial, what does that entail?

12 MR. PHILLIPS: Objection.

13 BY MR. DAVIS:

14 Q. Typically.

15 MR. PHILLIPS: Excuse me. Objection.

16 BY THE WITNESS:

17 A. Safety and efficacy, dose ranging.

18 BY MR. DAVIS:

19 Q. Three things typically?

20 MR. PHILLIPS: Objection.

21 BY THE WITNESS:

22 A. Depends on the trial.

23 BY MR. DAVIS:

24 Q. Typically when you have run Phase II

1 trials, you've been looking at safety, correct?

2 A. Correct.

3 Q. Efficacy?

4 A. Correct.

5 Q. And also trying to determine the

6 appropriate dosing?

7 A. Correct.

8 Q. And by safety, we mean whether it's just

9 safe to administer this drug to a human being, is

10 that right?

11 MR. PHILLIPS: Objection.

12 MR. DAVIS: I will withdraw the question.

13 BY MR. DAVIS:

14 Q. How do you describe safety? What do you

15 mean by safety?

16 A. Adverse event profile.

17 Q. What do you mean by "adverse event

18 profile"?

19 A. Adverse events associated with the drug.

20 Q. What is an adverse event?

21 MR. PHILLIPS: Objection.

22 BY MR. DAVIS:

23 Q. You understand here I'm asking for your

24 understanding of all of these terms.

1 A. Correct. I'm trying to think of the
2 best way to say it.

3 Q. And you are familiar with these terms,
4 correct?

5 A. Yes.

6 Q. If at any point in time I use a term
7 that you are not familiar with, please just tell me
8 that. Do you understand that? Are you agreeable
9 with that?

10 A. Yes.

11 Q. Going back to the question.

12 What is an adverse event?

13 A. It would be a sign or a symptom that may
14 need to be treated or may not. It's any complaint
15 the patient has regarding their health.

16 Q. Are adverse events in the course of
17 clinical trials generally regarded as undesirable?

18 MR. PHILLIPS: Objection.

19 BY THE WITNESS:

20 A. I don't think that -- no.

21 BY MR. DAVIS:

22 Q. Why are they called adverse events?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 A. I didn't name it.

2 BY MR. DAVIS:

3 Q. So, when you say that you're looking for
4 adverse events when you are checking the safety of
5 a drug in a clinical trial, are you looking for
6 adverse events that could cause you to believe the
7 drug is unsafe?

8 MR. PHILLIPS: Objection.

9 BY THE WITNESS:

10 A. Among other things.

11 BY MR. DAVIS:

12 Q. I need to understand from you what it is
13 that you are looking for by way of safety when you
14 run a clinical trial.

15 MR. PHILLIPS: Objection.

16 BY MR. DAVIS:

17 Q. You said you're looking for adverse
18 events, is that right?

19 A. Correct.

20 Q. Anything else, in terms of safety?

21 A. In terms of safety. Adverse events is a
22 big term. It could be lab values. There is
23 different types of adverse events. There is
24 serious adverse events and adverse events.

1 Q. So, there are different types -- you
2 said there are different types of adverse events.

3 Meaning serious adverse events are what?

4 A. We have a definition in our protocols
5 that states what are serious adverse events. I --
6 I couldn't -- hospitalization, death, among other
7 things. And I can't recall all -- right off the
8 top of my head.

9 Q. You made reference to protocols. What
10 is a protocol?

11 A. That is the template by which a study is
12 run.

13 Q. In your experience who typically drafts
14 the protocols for the clinical trials that you've
15 worked on?

16 A. It's a group effort.

17 Q. Do you participate in the drafting?

18 A. I do.

19 Q. Are you the primary author of the
20 clinical trial protocols on trials that you've
21 managed?

22 A. By primary author, I am the person that
23 would compile it, but I would not necessarily be
24 the person -- I wouldn't be the person who wrote

1 the statistics section or anything like that. I

2 would be the primary compiler.

3 Q. In your capacity as a manager of

4 clinical trials, is one of your duties to take

5 responsibility for seeing that the protocol is

6 compiled and created?

7 A. Yes.

8 MR. PHILLIPS: Objection.

9 BY MR. DAVIS:

10 Q. What does the protocol describe?

11 A. The protocol describes the background,

12 the objectives of the trial, how the trial is done,

13 how the data is to be collected.

14 Q. Anything else?

15 A. How the data is to be analyzed.

16 Q. Is it fair to say the protocol is

17 essentially the roadmap for the clinical trial?

18 MR. PHILLIPS: Objection.

19 BY THE WITNESS:

20 A. Among other things.

21 BY MR. DAVIS:

22 Q. What I said is accurate?

23 MR. PHILLIPS: Objection; misstates the

24 testimony.

1 MR. DAVIS: Trying to clarify the testimony.

2 BY THE WITNESS:

3 A. Could you say again?

4 BY MR. DAVIS:

5 Q. Yes, sure. Would it be fair to say that

6 the protocol is essentially the roadmap for the

7 clinical trial?

8 MR. PHILLIPS: Objection.

9 BY THE WITNESS:

10 A. Well, it certainly is the plan.

11 BY MR. DAVIS:

12 Q. Now, going back to the different phases.

13 You said that the three things you are looking for

14 in Phase II are safety, efficacy and also

15 appropriate dosing typically.

16 What are you looking for in Phase III?

17 A. Phase III are trials that include a

18 greater number of subjects, again, safety and

19 efficacy.

20 Q. Is there a difference between a

21 Phase III trial and a Phase II trial?

22 MR. PHILLIPS: Objection.

23 BY MR. DAVIS:

24 Q. In your experience.

1 A. Size.

2 Q. Anything else?

3 A. No.

4 Q. To your knowledge is it necessary for a
5 pharmaceutical compound to go through Phase I,
6 Phase II and Phase III trials in order to be
7 approved by the FDA?

8 MR. PHILLIPS: Objection.

9 BY THE WITNESS:

10 A. That would be a regulatory answer. I'm
11 not regulatory.

12 BY MR. DAVIS:

13 Q. You don't know?

14 A. I don't know.

15 Q. Have you ever worked on a compound that
16 went directly from Phase II into a new drug
17 application to the FDA?

18 A. I don't recall.

19 Q. You don't recall ever having that
20 happen?

21 A. Correct.

22 Q. You mentioned a moment ago that you
23 worked on a clinical trial M99-114. What trial was
24 that?

1 A. That was the diabetic neuropathy trial.

2 Q. Involving 594?

3 A. Yes.

4 Q. Approximately when was it that you
5 worked on that particular trial?

6 A. '99.

7 Q. Did you work on it beyond '99?

8 A. More than likely, yes. I don't know the
9 exact dates.

10 Q. What were your duties and
11 responsibilities with respect to that -- that
12 trial?

13 And by "that trial," I mean the 114
14 trial. If I refer to it as the 114 trial, you know
15 what I'm referring to, is that right?

16 A. Yes. Duties and responsibilities would
17 include managing the trial and that includes
18 managing the CRO, contract research organization,
19 troubleshooting the sites when they call and have
20 questions regarding the protocol, answering those
21 questions, making sure the data is captured and is
22 clean.

23 Q. Anything else?

24 A. Those are the main.

1 Q. You made reference earlier today that
2 part of your responsibilities as clinical project
3 manager include start-up of the trial. What does
4 that entail?

5 A. That entails hiring vendors, choosing
6 vendors, CROs, central labs. It entails
7 coordinating the protocol, writing informed
8 consent, choosing investigators, training
9 investigators. Everything it takes to get a study
10 up and running. Getting regulatory documents in,
11 shipping drug.

12 Q. You also made reference to closeout or
13 closing out a clinical trial. What does that
14 typically entail?

15 A. That typically entails pulling the CRFs,
16 case report forms, sending them -- having them sent
17 in, doing final drug accountability, cleaning the
18 database.

19 Q. Anything else?

20 A. That's what -- no.

21 Q. What do you mean, "cleaning the
22 database"?

23 A. A case report forms come in. There may
24 be incorrect information on them, not incorrect,

1 but blanks or items that don't make sense and
2 queries are sent out to the site to correct.
3 Investigator signs off on it, comes back in, an
4 addenda is made and all this is done prior to
5 opening the database.

6 Q. When you say "opening the database,"
7 what do you mean?

8 A. Unlocking. Unblinding.

9 Q. What does it mean to unblind a database?

10 A. To unblind the database is to know what
11 the subject was taking so that statistical analysis
12 can be done.

13 Q. So, unblinding means at that point in
14 time the people who are running the trial can look
15 at and determine precisely what it was -- what
16 compound or placebo or whatever material a
17 particular patient was taking, is that right?

18 A. Correct.

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. And the database is locked after it's
22 cleaned and it's not unblinded until it's locked.

23 BY MR. DAVIS:

24 Q. By "locked" means that no one else can

1 make further changes to the database?

2 A. Correct.

3 Q. In your experience when is a typical --

4 when is a clinical trial typically regarded as

5 having ended?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. I guess it depends on which group you're

9 talking of. For me it's ended when the database

10 locks.

11 BY MR. DAVIS:

12 Q. Do you typically participate in the

13 analysis of the data once the database has been

14 locked and unblinded?

15 A. I do not.

16 Q. Is the end of a clinical trial in your

17 view the same as ending enrollment in the clinical

18 trial?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. No.

22 BY MR. DAVIS:

23 Q. What does it mean to end enrollment in a

24 clinical trial?

1 A. No further patients are randomized.

2 Q. Does that mean that no additional

3 subjects or patients will be added to the clinical

4 trial?

5 A. Yes.

6 Q. We already talked for a few minutes

7 about adverse events. Your testimony is that

8 adverse events can be positive and negative with

9 respect to a clinical trial, is that right?

10 MR. PHILLIPS: Objection; mischaracterizes the

11 testimony. Well, objection.

12 MR. DAVIS: You can state the word

13 "Objection." That would be appreciated.

14 MR. PHILLIPS: I beg your pardon?

15 MR. DAVIS: If you could just state the word

16 "Objection," that would be appreciated. We went

17 through this earlier and if you think that there is

18 further clarification necessary, I'd be more than

19 happy to ask for it but the word "Objection" will

20 suffice.

21 MR. PHILLIPS: Mr. Davis, I will proceed in

22 depositions as I think appropriate and I don't need

23 instruction from you. So, thank you very much.

24 MR. DAVIS: I will just point out again that

1 our practice in Massachusetts is that if you go and
2 state more than the word "Objection," you are
3 obstructing the deposition and I will stand by that
4 local practice.

5 So I ask you, please, if you have an
6 objection, you may state it. State the word
7 "Objection." But please do not state the basis for
8 your objection.

9 MR. PHILLIPS: I will do exactly as I feel is
10 appropriate and I'm sure that I will comply with
11 the local rules, Mr. Davis. Again, please do not
12 lecture me.

13 MR. DAVIS: I'm not lecturing you.

14 MR. PHILLIPS: Okay. Let's proceed with the
15 deposition.

16 MR. DAVIS: I made a request.

17 MR. PHILLIPS: Fine. I heard your request. I
18 will try to abide by it when possible.

19 BY MR. DAVIS:

20 Q. Ms. Collicott, what do you understand to
21 be adverse events?

22 MR. PHILLIPS: Objection.

23 BY THE WITNESS:

24 A. An adverse event can be anything from a

1 runny nose to a death and anything in between.

2 BY MR. DAVIS:

3 Q. Is an adverse event in your experience a

4 desired outcome of a clinical trial?

5 MR. PHILLIPS: Objection.

6 BY THE WITNESS:

7 A. No.

8 BY MR. DAVIS:

9 Q. Is it fair to say that in running a

10 clinical trial at Abbott, for example, you're not

11 looking to bring about adverse events, is that

12 right?

13 MR. PHILLIPS: Objection.

14 BY THE WITNESS:

15 A. Adverse events occur. There would be no

16 clinical trial without adverse events. So, it's

17 part and parcel of running a clinical trial.

18 BY MR. DAVIS:

19 Q. My question was a little bit different

20 in that you stated you have an objective for a

21 clinical trial, is that right, typically?

22 A. Yes.

23 Q. Is it one of the objectives of the

24 clinical trial to bring about adverse events in

1 your experience?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. Objectives of the trial are to determine

5 safety and efficacy.

6 BY MR. DAVIS:

7 Q. And is it -- have you ever had a

8 clinical trial that you've participated in which

9 one of the objectives of the trial was to bring

10 about adverse events?

11 MR. PHILLIPS: Objection.

12 BY THE WITNESS:

13 A. Not to my knowledge.

14 BY MR. DAVIS:

15 Q. Would it be fair to say that you would

16 be perfectly happy if you run a clinical trial and

17 there were no adverse events in the course of that

18 trial?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. I would not be happy.

22 BY MR. DAVIS:

23 Q. Why not?

24 A. Because then the trial is run wrong.

1 There is something wrong if there is no adverse
2 events.

3 Q. Would it be fair to say that in running
4 a clinical trial, the fewer adverse events, the
5 more positive you think that outcome to be?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. I wouldn't say that. I would say it all
9 depends on the trial. Having fewer adverse events
10 doesn't necessarily mean a positive trial.

11 BY MR. DAVIS:

12 Q. And by "positive trial" you mean what?

13 A. Final results are positive. Safety,
14 efficacy.

15 Q. Have been demonstrated?

16 A. Would have been statistically
17 significantly demonstrated.

18 Q. Have you heard the term "premature
19 termination" in the course of clinical trials?

20 A. Yes.

21 Q. What does that mean?

22 MR. PHILLIPS: Objection.

23 BY THE WITNESS:

24 A. It means a patient drops prior to

1 completion of the study.

2 BY MR. DAVIS:

3 Q. Meaning the patient ceases to

4 participate in the study prior to the date in which

5 the study would call for that patient to cease

6 participation, is that right?

7 MR. PHILLIPS: Objection.

8 BY THE WITNESS:

9 A. Correct.

10 BY MR. DAVIS:

11 Q. Is the -- in your experience is

12 premature termination the same as early

13 termination?

14 A. Yes.

15 Q. And to your knowledge, is your

16 understanding of those terms consistent with the

17 way those terms are used within Abbott?

18 MR. PHILLIPS: Objection.

19 BY THE WITNESS:

20 A. Yes.

21 BY MR. DAVIS:

22 Q. Now, I may botch this. Are you familiar

23 with the term "emesis"?

24 A. I think you botched it.

1 Q. I wouldn't be shocked.

2 A. Could you spell it?

3 Q. E-m-e-s-i-s.

4 A. Emesis, yes.

5 Q. I will acknowledge on the record that I

6 botched it.

7 What is emesis?

8 A. Vomiting.

9 Q. Have you heard the term "emesis

10 liability"?

11 A. I have not.

12 Q. Is emesis an adverse event in a clinical

13 trial?

14 A. Depends on the clinical trial.

15 Q. For example, in 594 clinical trials that

16 you participated in, was emesis regarded as an

17 adverse event?

18 MR. PHILLIPS: Objection.

19 BY THE WITNESS:

20 A. Yes. Yes.

21 BY MR. DAVIS:

22 Q. Have you heard the term "commercial

23 viability" in the context of clinical trials?

24 A. No.

1 Q. Just going back over your
2 responsibilities so we have it clearly delineated.
3 Is it fair to say that you help organize
4 the trials, help plan the trials, implement the
5 trials and carry them through to the point where,
6 as you mentioned, the database, the data has been
7 collected, cleaned to the extent possible and the
8 database is locked?

9 MR. PHILLIPS: Objection.

10 BY THE WITNESS:

11 A. That's correct.

12 BY MR. DAVIS:

13 Q. At that point in time would your
14 responsibility with respect to that trial typically
15 be over?

16 A. Again, it depends on the trial. Depends
17 on the group.

18 Q. Typically?

19 A. Typically it would be over.

20 Q. At that point in time you would move on
21 to a new project, a different clinical trial, is
22 that right?

23 A. I may or may not. It depends on the
24 group. It depends -- every group has different

1 ideas on how things work.

2 Q. In your experience is there data

3 available from a clinical trial before it has -- is

4 there data available to the sponsor of the clinical

5 trial before the trial has been unblinded?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. Before it's been unblinded?

9 Q. Yes.

10 A. There's blinded data available.

11 Q. What is blinded data?

12 A. You may see -- PS report forms are

13 collected. Lab results are collected. So you

14 would see information but you would not know

15 anything about the patients, what they were on,

16 what they were randomized to. You have no idea.

17 Q. So you don't know what the patients, for

18 example, are taking, is that right?

19 A. Correct.

20 Q. But would you know, for example, before

21 a trial is unblinded whether a particular patient

22 has experienced adverse events?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 A. You would know that.

2 BY MR. DAVIS:

3 Q. Would you know whether a patient has
4 terminated early?

5 A. Yes.

6 Q. So that data is available before the
7 study is unblinded, is that right?

8 A. Yes.

9 MR. PHILLIPS: You're speaking typically,
10 Mr. Davis.

11 MR. DAVIS: Yes.

12 BY THE WITNESS:

13 A. Typically.

14 MR. DAVIS: Based on her experience within
15 Abbott.

16 BY THE WITNESS:

17 A. That's correct.

18 BY MR. DAVIS:

19 Q. Other terms I just want to ask you
20 about. Are you familiar with a term
21 "tolerability"?

22 A. Yes.

23 Q. What do you understand that to be in the
24 context of a clinical trial?

1 A. To me it means if a patient can tolerate

2 a drug.

3 Q. What does it mean to tolerate a drug?

4 MR. PHILLIPS: Objection.

5 BY THE WITNESS:

6 A. To tolerate a drug -- I -- can you

7 rephrase that?

8 BY MR. DAVIS:

9 Q. Yes. You mentioned a moment ago that to

10 you tolerability means if a patient can tolerate a

11 drug?

12 A. Um-hmm.

13 Q. And my question to you is: What do you

14 mean tolerate a drug?

15 A. Not have serious adverse events related

16 to the drug.

17 Q. Is it fair to say that in your

18 experience tolerability, the ability of a patient

19 not to experience adverse events, is a desirable

20 outcome --

21 MR. PHILLIPS: Objection.

22 BY MR. DAVIS:

23 Q. -- of a clinical trial?

24 MR. PHILLIPS: Objection.

1 participated in any clinical trials in which one of
2 the objectives of the trial was to determine
3 whether a particular drug or compound was well
4 tolerated?

5 MR. PHILLIPS: Objection.

6 BY THE WITNESS:

7 A. I don't recall. Not those words.

8 BY MR. DAVIS:

9 Q. Well, has tolerability ever been --
10 determining tolerability of a drug ever been one of
11 the objectives of a clinical trial in which you've
12 participated?

13 A. Safety and efficacy.

14 Q. You regard tolerability as a subset of
15 safety or efficacy?

16 MR. PHILLIPS: Objection.

17 BY THE WITNESS:

18 A. I don't know if I would. It's a very
19 gray area.

20 BY MR. DAVIS:

21 Q. Is tolerability one of the things that
22 you typically measure in the course of clinical
23 trials?

24 MR. PHILLIPS: Objection.

1 BY THE WITNESS:

2 A. You measure safety, certainly you
3 measure safety. I don't know if there would be a
4 term that says we are measuring tolerability. We
5 are measuring safety.

6 BY MR. DAVIS:

7 Q. Is tolerability one of the things that
8 you typically keep track of in the course of
9 clinical trials?

10 MR. PHILLIPS: Objection.

11 BY THE WITNESS:

12 A. Well, that would be -- that would be
13 somewhat linked to adverse events and we do keep
14 track of adverse events.

15 BY MR. DAVIS:

16 Q. Do adverse events tell you whether the
17 compound is being tolerated or well tolerated in
18 the course of the trial?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. They may or they may not.

22 BY MR. DAVIS:

23 Q. Is that what you would look to to
24 determine tolerability? Would you look to adverse

1 events?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. It would be one of the -- it would be

5 something I would look at.

6 BY MR. DAVIS:

7 Q. What else would you look at to determine

8 how well tolerated the compound or drug is?

9 MR. PHILLIPS: Objection.

10 BY THE WITNESS:

11 A. That would be the main thing.

12 BY MR. DAVIS:

13 Q. That being adverse events?

14 A. Adverse events.

15 Q. Are you familiar with the term

16 "titration"?

17 A. Yes.

18 Q. What is your understanding of the

19 meaning of the term "titration" as used in clinical

20 trials?

21 A. My understanding is titration is being a

22 gradual increase or a decrease of a dose.

23 Q. Over the course of the trial?

24 A. Yes.

1 A. I'm familiar with the acronym. It's no
2 longer used. And I don't remember what it means.

3 Q. Are you familiar with the term
4 "outlicense"?

5 A. I'm familiar with the term.

6 Q. Have your responsibilities at Abbott
7 ever involved outlicensing of any compounds?

8 A. No.

9 Q. In the context of your work on 594, I
10 just want to ask you the names of some people and
11 ask you what roles they played to your knowledge.

12 Are you familiar with Mr. Bruce
13 McCarthy?

14 A. Yes.

15 Q. What role, if any, did Mr. McCarthy play
16 in clinical trials involving 594?

17 MR. PHILLIPS: It's actually Dr. McCarthy.

18 MR. DAVIS: That's fine.

19 BY THE WITNESS:

20 A. Associate medical director.

21 BY MR. DAVIS:

22 Q. What does that mean? What were his
23 duties and responsibilities?

24 A. I couldn't tell you exactly what his

1 duties and responsibilities are.

2 Q. What did you observe him do with respect

3 to --

4 A. He was the medical director.

5 Q. What did the medical director do with

6 respect to clinical trials?

7 MR. PHILLIPS: Objection.

8 BY THE WITNESS:

9 A. You know, he worked at a different level

10 than I did. So, I don't really know what his

11 duties, day-to-day duties were.

12 BY MR. DAVIS:

13 Q. You have no further knowledge on what

14 his duties were with respect to clinical trials

15 involving 594?

16 A. No.

17 Q. Who was your immediate superior on the

18 114 trial?

19 A. Bruce McCarthy.

20 Q. One of the things he did was supervise

21 you?

22 A. Yes.

23 Q. Did you meet with him periodically?

24 A. Yes.

1 Q. How frequently in the course of that
2 trial?

3 A. There would have been a range of times,
4 but I would say as an average, every couple of
5 weeks.

6 Q. Were these face-to-face meetings?

7 A. Sometimes.

8 Q. Were most of the meetings face-to-face
9 meetings?

10 A. Yes.

11 Q. In the course of meetings would you
12 report on the status of the clinical trial?

13 A. Yes.

14 Q. What things would you tell Mr. McCarthy?
15 What kinds of information would you provide to him
16 in the course of these meetings?

17 A. If we were in the start-up phase, I
18 would be advising him as to where we were as far as
19 collecting documents, identifying investigators.
20 If it was during the trial, I would have been
21 speaking about enrollment. I would have contacted
22 him if I had received a call from a site
23 questioning something about the protocol that I
24 didn't know the answer to.

1 Q. Anything else?

2 A. Not really.

3 Q. Would you inform him of adverse events?

4 A. Serious adverse events. He would have
5 been informed about that.

6 Q. Did you regard emesis as a serious
7 adverse event in the course of the 114 trial?

8 MR. PHILLIPS: Objection.

9 BY THE WITNESS:

10 A. I have to qualify that. No. That would
11 not be considered a serious adverse event unless it
12 had met one of our serious adverse event criteria,
13 which would be life threatening, you know.

14 BY MR. DAVIS:

15 Q. Would you keep Mr. McCarthy advised on
16 the enrollment data?

17 A. Yes.

18 Q. Would you keep Mr. McCarthy advised on
19 any premature terminations?

20 A. I believe so, yes.

21 Q. Including the rate of premature
22 terminations?

23 A. I would just have -- we would just
24 generally, say, give an update saying here is our

1 enrollment. It was mainly the enrollment numbers.
2 That was the most important, not so much the
3 premature terminations, as reaching enrollment
4 numbers.
5 Q. Is it fair to say that in putting
6 together a clinical trial and creating the
7 protocol, one of the things that would be
8 established would be a target number of subjects or
9 patients for the trial?
10 A. Yes.
11 Q. Part of your job was to try to ensure
12 that the trial would reach that appropriate number
13 of subjects or patients?
14 A. Yes.
15 Q. Do you have any understanding of what
16 would happen to the trial if you did not reach the
17 targeted number of subjects or patients?
18 MR. PHILLIPS: Objection.
19 BY THE WITNESS:
20 A. It depends on the trial. That happens
21 quite often, not to make enrollment. How it
22 affects the trial as far as analytically, whatever,
23 I don't know, because that's not my job.
24 BY MR. DAVIS:

1 Q. You have said you have handled
2 approximately 15 clinical trials. How many of
3 those have failed to reach the targeted number of
4 subjects or patients?

5 A. Ooh, I'd say about half.

6 Q. And how many of those have you ended
7 enrollment early?

8 A. By ended "enrollment early," do you mean
9 before its scheduled end date or do you mean
10 stopped enrollment early?

11 Q. Before its scheduled end date.

12 A. So, how many of the trials that did not
13 meet enrollment did I participate in --

14 Q. I will rephrase the question.

15 A. Please do, yeah.

16 Q. How many clinical trials that you've
17 been responsible for managing did you end
18 enrollment prior to the scheduled end enrollment
19 date?

20 A. I don't remember exact number, but there
21 have been a few.

22 Q. The 114 trial was one such trial,
23 correct?

24 A. I don't remember exactly. We may have

1 extended the enrollment and then -- there is so --
2 with the clinical trials, we -- this is a general
3 statement -- is we often extend enrollment times
4 and dates to allow to get the patients in that we
5 need.

6 We may have done that, extended the
7 original date, and then ended it early, which
8 technically wouldn't have been early if you looked
9 at the original date, if you know what I'm saying.

10 Q. Going back to my question.

11 A. Yes.

12 Q. Okay. How many clinical trials that you
13 were involved in at Abbott have you ended
14 enrollment prior to the scheduled enrollment date?

15 MR. PHILLIPS: Objection.

16 BY THE WITNESS:

17 A. I don't recall.

18 BY MR. DAVIS:

19 Q. More than one?

20 A. I don't recall.

21 Q. Who was Mr. McCarthy's immediate
22 superior when you were working on the 114 trial?

23 A. Chris Silber.

24 Q. Did you periodically meet with

1 Mr. Silber?

2 A. Yes.

3 Q. Is he a doctor?

4 A. Yes.

5 Q. Did you provide Mr. Silber with an

6 update on the trial?

7 MR. PHILLIPS: Objection.

8 BY MR. DAVIS:

9 Q. At these periodic meetings.

10 A. I may have.

11 Q. Do you recall whether you did?

12 A. I don't recall.

13 Q. For what purpose did you meet with

14 Mr. -- Dr. Silber?

15 A. Just to touch base. My main --

16 information from -- to Dr. Silber would have come

17 from Dr. McCarthy. But --

18 Q. I'm sorry. You say your information to

19 Dr. Silber would have come from Dr. McCarthy. What

20 do you mean?

21 A. Well, Dr. McCarthy reported to

22 Dr. Silber. So therefore they would have had

23 one-on-ones. My meetings with Dr. Silber were not

24 necessarily in the context of the trial. You know,

1 he was the venture head. He would touch base with
2 all the people in the department for meetings, see
3 how things were going.

4 Q. What venture was Dr. Silber the head of?

5 A. Analgesia.

6 Q. That analgesia venture that we mentioned
7 earlier this morning?

8 A. Yes.

9 Q. Do you know Mr. Michael -- I apologize
10 for butchering this up front -- Biarnesen?

11 A. Biarnesen.

12 Q. You do know Mr. Biarnesen?

13 A. Yes, I do.

14 Q. Is he a doctor?

15 A. No.

16 Q. Did Mr. Biarnesen play any role in any
17 594 clinical trials?

18 A. He was operations manager.

19 Q. What are the responsibilities of
20 operations manager?

21 MR. PHILLIPS: Objection.

22 BY THE WITNESS:

23 A. I couldn't really tell you what his
24 responsibilities were.

1 responsibility for managing that trial?

2 A. I don't remember. I don't remember.

3 Q. How far into the trial was it?

4 A. I don't remember.

5 Q. Had they began enrolling patients when

6 you took over responsibility for the trial?

7 A. I don't remember. I'm sorry.

8 Q. You also made reference to an M99-115

9 trial?

10 A. Yes.

11 Q. Involving 594?

12 A. Yes.

13 Q. Were you in charge of that trial?

14 A. I was.

15 Q. And was that trial actually conducted by

16 Abbott?

17 A. No.

18 Q. That was a trial that was planned at

19 some point in time but not actually undertaken by

20 Abbott, is that right?

21 A. Correct.

22 Q. How far did that trial get?

23 A. I don't recall.

24 Q. Did they begin enrolling patients?

1 A. No.

2 Q. Was there a protocol written?

3 A. I don't remember.

4 Q. In your experience is the protocol for a
5 clinical trial an actual written document?

6 A. Yes, it is.

7 Q. Was there a written protocol for the 114
8 trial?

9 A. I don't remember if we got that far. I
10 don't remember.

11 Q. For the 114 trial?

12 MR. PHILLIPS: Listen to the question.

13 THE WITNESS: I'm sorry.

14 MR. PHILLIPS: I think you misheard.

15 (WHEREUPON, the record was read
16 by the reporter as requested.)

17 BY THE WITNESS:

18 A. Oh, I'm sorry. I did. I'm sorry.

19 BY MR. DAVIS:

20 Q. I will ask the question again.

21 Was there a written protocol for the 114
22 trial?

23 A. Yes.

24 Q. Did you have a copy of that?

1 A. Did I have a copy of it?

2 Q. Yes.

3 A. While I was working on the trial?

4 Q. Correct.

5 A. Yes.

6 Q. And what did it look like?

7 A. It looks like a bunch of papers.

8 Q. Was it a binder of some sort?

9 A. No, usually not.

10 Q. How many pages approximately?

11 A. Can vary, so I don't know for this

12 particular one.

13 Q. You have no recollection of how many

14 pages that trial was?

15 A. No.

16 Q. How thick a document was it?

17 A. How thick?

18 Q. Yes.

19 A. (Indicating.)

20 Q. About --

21 A. Half inch, three-quarters of an inch.

22 MR. DAVIS: Why don't we mark this as the next

23 exhibit, please.

24 (WHEREUPON, a certain document was

1 marked Collicott Deposition Exhibit

2 No. 2, for identification, as of

3 09-27-2006.)

4 MR. DAVIS: Greg, you can see the way I

5 typically run my depositions, I will bring a

6 courtesy copy of the exhibit for you. I'd ask that

7 in depositions that you folks take that you do the

8 same for us if possible.

9 MR. PHILLIPS: I would assume we intend to do

10 that.

11 BY MR. DAVIS:

12 Q. Ms. Collicott, you have what has been

13 marked as Exhibit 2. Would you look at that

14 document for a moment and tell me first if you have

15 seen it before.

16 A. I don't recall.

17 Q. As you sit here today do you recall

18 playing any role in helping to develop a -- put

19 together a development plan or an executive summary

20 for ABT-594?

21 A. I would not.

22 Q. Did you have any involvement in any

23 Phase I studies for ABT-594?

24 A. No.

1 Q. Did you review any data for -- from the
2 Phase I studies for 594 before you participated in
3 any Phase II studies for 594?

4 A. No.

5 Q. Would you take a look, please, at the
6 page -- and you are going to see in the documents
7 that each document has what we call a Bates
8 number --

9 A. Okay.

10 Q. -- typically in the lower right-hand
11 corner.

12 A. Okay.

13 Q. This one begins with ABBT. Would you
14 look at the Bates number that ends 9030, please.

15 MR. PHILLIPS: I'm sorry. I missed the Bates
16 number.

17 MR. DAVIS: Sure. It's 9030.

18 MR. PHILLIPS: Thank you.

19 BY THE WITNESS:

20 A. Yes.

21 Q. You should be on a page that is titled
22 at the top "D.2 Registration Trial." Do you see
23 that?

24 A. Yes.

1 Q. This is a discussion of Phase I trials
2 involving ABT-594 and if you look in the third
3 paragraph down it says, "For the ABT-594 oral
4 solution."

5 Do you see that paragraph?

6 A. Yes.

7 Q. In that paragraph it discusses -- take a
8 moment, please, and read the paragraph and tell me
9 when you're done.

10 A. Okay.

11 Q. First, this paragraph indicates that
12 adverse events experienced in a Phase I trial of
13 ABT-594 included dizziness, nausea and vomiting.
14 Do you see that?

15 A. Yes.

16 Q. Were those considered adverse events for
17 purposes of any of the Phase II trials that you ran
18 for 594?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. I'm -- were they considered adverse
22 events?

23 Q. Yes.

24 A. Because here they are listed as adverse

1 events.

2 Q. I understand that. This is the Phase I

3 trial.

4 A. Oh.

5 Q. My question is for purposes of your

6 Phase II trials involving 594, did you consider

7 dizziness, nausea and vomiting to be adverse

8 events?

9 A. Well, it wouldn't be for me to consider,

10 but they were reported as adverse events.

11 Q. A few moments ago we talked about

12 emesis?

13 A. Um-hmm.

14 Q. Emesis is the same as vomiting as far as

15 you know?

16 A. As far as I know.

17 Q. In running the 594 Phase II trials, was

18 vomiting, emesis, nausea, were those things that

19 you were particularly sensitive to or looking out

20 for in the course of the trial?

21 MR. PHILLIPS: Objection.

22 BY THE WITNESS:

23 A. No.

24 BY MR. DAVIS:

1 Q. Did you in running any Phase II trials
2 for 594 at Abbott, did you ever have any
3 discussions with anyone at Abbott about concerns
4 that people within Abbott had regarding the
5 tolerability of 594?

6 A. No.

7 Q. Never had any discussions on that topic
8 with anybody at Abbott?

9 A. Not that I recall.

10 Q. Did you ever hear anyone within Abbott
11 refer to any tolerability problems with 594?

12 A. Not that I recall.

13 Q. Are you familiar with a molar extraction
14 study that was conducted with respect to 594?

15 A. I heard of it.

16 Q. Did you play any role in that study?

17 A. I did not.

18 Q. Did you review any of that data before
19 you participated in any Phase II trials for 594?

20 A. I did not review it.

21 MR. DAVIS: Let's mark this as the next
22 exhibit, please, Exhibit 3.

23 (WHEREUPON, a certain document was
24 marked Collicott Deposition Exhibit

1 BY THE WITNESS:

2 A. I don't -- I don't know for sure
3 because, you know, that's actually done by the
4 Federal Government.

5 BY MR. DAVIS:

6 Q. Is that consistent with your
7 understanding?

8 A. I'm not sure.

9 Q. Okay.

10 MR. DAVIS: Mark this as the next exhibit,
11 please.

12 (WHEREUPON, a certain document was
13 marked Collicott Deposition Exhibit
14 No. 4, for identification, as of
15 09-27-2006.)

16 MR. PHILLIPS: Just to be make sure I'm
17 understanding the way in which you intend to mark
18 Deposition Exhibits. You are going to start a new
19 number with each deposition.

20 MR. DAVIS: Correct.

21 MR. PHILLIPS: As opposed to doing all -- all
22 Plaintiff's Deposition Exhibits in order.

23 MR. DAVIS: Correct.

24 MR. PHILLIPS: Okay. Just want to make sure I

1 understand.

2 MR. DAVIS: When we get to trial, the way the
3 Courts typically ask that we handle it is we put
4 together a list of exhibits and we can number them
5 for purposes of trial.

6 MR. PHILLIPS: That's fine. I just wanted to
7 make sure I was understanding what you meant.

8 BY MR. DAVIS:

9 Q. You have what has been marked as
10 Exhibit 4. Have you seen this document before?

11 A. Yes, I have.

12 Q. What is it?

13 A. It's an IND annual report.

14 Q. What is an IND annual report?

15 A. It's an update to -- to the IND that
16 updates information from a certain time frame, from
17 the previous year.

18 Q. What's the purpose of the report?

19 A. I honestly don't know the purpose of the
20 report other than to just update the safety.

21 Q. Do you understand that these reports are
22 something that pharmaceutical companies that are
23 engaged in development must file with the FDA?

24 MR. PHILLIPS: Objection.

1 BY THE WITNESS:

2 A. I can't speak to other companies. I

3 don't know if it's a federal requirement.

4 BY MR. DAVIS:

5 Q. Do you know if it's required at all?

6 A. I don't know.

7 Q. On the second page of this document,

8 it's got a signature line for you, correct?

9 A. Yes.

10 Q. Did you participate in the drafting of

11 this report?

12 A. I participated in compiling it.

13 Q. What did you do in that regard?

14 A. If I could just look through it quickly.

15 I would have pulled together the

16 information for the introduction as to how many

17 open IND's there were, what studies were included

18 in this report. I would have written the

19 individual study information and I would have just

20 pulled that right from the protocol. If results

21 were already written in a final report, I would

22 have pulled study results from a final report.

23 Otherwise I would have put it as pending. I did

24 not write final reports.

1 BY MR. DAVIS:

2 Q. You don't know one way or the other?

3 A. I don't.

4 Q. What does it mean to sign off on a
5 protocol?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. It means that the author and the
9 approvers sign it.

10 BY MR. DAVIS:

11 Q. Meaning that it's complete?

12 A. Yes.

13 Q. A little further down in the same
14 section there is a reference to "M99-114
15 (Neuropathic Pain) investigator meeting."

16 Do you see that?

17 A. Yes.

18 Q. It also says target date of February 25,
19 2000, completed?

20 A. Um-hmm.

21 Q. Did you conduct an investigator meeting
22 with respect to the 114 trial?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 A. Yes.

2 Q. What is an investigator meeting?

3 A. It's a meeting where we review the
4 protocol with all the PIs, principal investigators,
5 their coordinators. If any training needs to be
6 done, explanations on pieces of the protocol, this
7 is done during an investigator meeting.

8 Q. What is a neuropathic pain?

9 MR. PHILLIPS: Objection.

10 BY THE WITNESS:

11 A. It's not my area of expertise so I
12 really don't know.

13 BY MR. DAVIS:

14 Q. As you sit here today do you have any
15 knowledge of what neuropathic pain is?

16 A. Nerve ending pain.

17 Q. You made reference to the investigators.
18 What roles do the investigators play in a clinical
19 trial?

20 A. They are responsible for running the
21 trial at their site.

22 Q. Is it fair to say that they are --
23 oftentimes there is more than one investigator for
24 a clinical trial?

1 A. At a site?

2 Q. No. More than one investigator.

3 A. For the entire clinical trial?

4 Q. Yes.

5 A. Yes.

6 Q. And clinical trials oftentimes have work

7 going on at multiple locations, is that right?

8 A. Yes.

9 Q. How many different investigation sites

10 did the 114 trial have?

11 A. I don't recall.

12 Q. More than ten?

13 A. More than ten.

14 Q. How were the sites selected?

15 MR. PHILLIPS: Objection.

16 BY THE WITNESS:

17 A. I don't honestly remember how the sites

18 were selected.

19 BY MR. DAVIS:

20 Q. How are sites typically selected in your

21 experience?

22 MR. PHILLIPS: Objection.

23 BY THE WITNESS:

24 A. Key opinion leaders.

1 BY MR. DAVIS:

2 Q. What do you mean "key opinion leaders"?

3 A. Experts in the field of whatever we are

4 studying.

5 Q. What do you mean, experts in the field?

6 A. Doctors.

7 Q. But how do they play a role in selecting

8 of --

9 A. Oh, they don't. They don't. We may use

10 them as investigators. Key opinion leaders.

11 Q. How do you identify who the key opinion

12 leaders are?

13 MR. PHILLIPS: Objection.

14 BY THE WITNESS:

15 A. I don't. I don't identify.

16 BY MR. DAVIS:

17 Q. Well, did your duties as project or

18 clinical trial manager include identifying and

19 enrolling investigators for the trial?

20 A. Not identifying, but working to get them

21 up and running.

22 Q. Who was -- who within Abbott was

23 responsible for identifying the investigators for

24 the 114 trial?

1 the bottom of the first page it says under "Current
2 Month (April)" --

3 A. Um-hmm.

4 Q. -- it says, "First patient enrolled
5 Phase IIb."

6 Do you see that?

7 A. Yes.

8 Q. The Phase IIb trial, was that a -- was
9 that the 114 trial?

10 A. I don't know if that's what they're
11 referring to.

12 Q. Did you recall that you enrolled the
13 first patient in the 114 trial in or about April of
14 2000?

15 A. I do not remember.

16 Q. Is that something that would have been
17 reported to you?

18 A. When the first patient was enrolled?

19 Q. Correct.

20 A. I would have known at the time. I can't
21 remember now.

22 Q. How frequently did you track patient
23 enrollment statistics during the course of that
24 trial?

1 A. I tracked patient enrollment weekly.

2 Q. Did you encounter any problems with

3 patient enrollment in that trial?

4 MR. PHILLIPS: Objection.

5 BY THE WITNESS:

6 A. Which trial was that again?

7 Q. 114.

8 A. I don't recall. I don't recall. I have

9 done a lot of trials.

10 Q. If you take a look at the page of

11 Exhibit 6 that is numbered 4, the Bates number ends

12 4412.

13 A. Yes.

14 Q. Under the section under "Patent," do you

15 see "Progress," the very bottom of that section it

16 says, "3 to 5 compounds to be chosen as follow-on

17 to ABT-594 by May 2000. Of these three to five

18 compounds, one will be chosen in July/August for

19 Quarter 4 2000 DDC."

20 Do you see that?

21 A. Yes.

22 Q. First, do you know what a follow-on

23 compound is?

24 A. No.

1 Q. Did anyone at Abbott ever talk to you
2 about any follow-on compounds for ABT-594 or
3 potential follow-on compounds?

4 A. Not that I recall.

5 Q. Do you know what DDC is?

6 A. I don't know the -- I don't know the
7 term.

8 Q. Have you ever seen any reference to it
9 before within Abbott?

10 A. I have seen the reference before, yes.

11 Q. You just don't know what it is?

12 A. I don't know what it means.

13 MR. DAVIS: Let's mark this as the next
14 exhibit, please, 7.

15 (WHEREUPON, a certain document was
16 marked Collicott Deposition Exhibit
17 No. 7, for identification, as of
18 09-27-2006.)

19 BY MR. DAVIS:

20 Q. Ms. Collicott, you have what's been
21 marked Exhibit 7. Let me ask if you have seen this
22 document before?

23 A. I don't remember this.

24 Q. Did you report on a monthly basis to

- 1 someone within Abbott regarding the status of the
- 2 114 clinical trial?
- 3 A. Status in what regard?
- 4 Q. Status in any regard.
- 5 A. I would have given status updates at --
- 6 yes, yes.
- 7 Q. To who?
- 8 A. Bruce McCarthy.
- 9 Q. And would you give them to him at those
- 10 meetings that you referred to earlier today?
- 11 A. Yes.
- 12 Q. This document states as of June 2000,
- 13 near the top it says, "Enrollment in MM" -- I'm
- 14 sorry -- "in M99-1114 is slower than planned and is
- 15 under scrutiny by team personnel. (See
- 16 July Progress Gauges below.)"
- 17 Do you see that? Do you see that
- 18 reference?
- 19 A. No, I'm actually looking for it. Where
- 20 is it?
- 21 Q. Up near the top, the second bullet
- 22 point.
- 23 A. Oh, I'm sorry. Yes, I see it.
- 24 Q. Do you recall that enrollment in the 114

1 trial as of June 2000 was deemed by Abbott to be

2 slower than planned?

3 MR. PHILLIPS: Objection.

4 BY THE WITNESS:

5 A. It's -- it's hard for me to recall

6 whether that is specifically the date that that

7 occurred. I can't remember.

8 BY MR. DAVIS:

9 Q. Do you recall at any point in time you

10 deemed the enrollment in the 114 trial to be slower

11 than planned?

12 MR. PHILLIPS: Objection.

13 BY THE WITNESS:

14 A. Yes.

15 BY MR. DAVIS:

16 Q. When did -- as best you recall here

17 today, when did you first come to believe that the

18 enrollment of subjects or patients in that trial

19 was going slower than planned?

20 A. I don't know.

21 Q. Did you play any role in addressing that

22 issue within Abbott?

23 A. Yes.

24 Q. Did that -- the fact that you were

1 enrolling patients slower than planned, did that
2 cause you any concern?

3 A. Not particularly. It's a common
4 occurrence.

5 Q. Now, further down on the same page it
6 says, "Contact all M99-114 investigators to
7 determine enrollment obstacles."

8 Did you participate in that process?

9 MR. PHILLIPS: I'm sorry, Mr. Davis. I'm not
10 sure I saw -- oh, I see. I'm sorry. I see it.

11 BY THE WITNESS:

12 A. I don't recall what I particularly would
13 have done.

14 BY MR. DAVIS:

15 Q. Do you have any recollection as you sit
16 here today what, if anything, you did in response
17 to realizing that enrollment in the 114 study was
18 going slower than planned?

19 A. I would be speculating as to what I
20 would do now; but what I actually did at the time,
21 I don't recall.

22 Q. There is a reference on this page to
23 "Review early terminations and Adverse Event
24 profile to determine strategic options to address

1 slow enrollment."

2 Do you see that?

3 A. Yes.

4 Q. At some point in time did you come to

5 understand that the slow enrollment in the 114

6 trial was due at least in part to premature

7 terminations?

8 A. No.

9 Q. Did you come to believe that it was

10 attributable at least in part to early

11 terminations?

12 A. No.

13 Q. That is something you never came to

14 realize?

15 A. No, because enrollment has nothing to do

16 with early terminations.

17 Q. Did you participate at all in any review

18 of early terminations and adverse event profile

19 data to determine strategic options to address slow

20 enrollment?

21 A. No.

22 Q. Who within Abbott did that, if you know?

23 A. I don't know.

24 Q. Did you make any recommendations or

1 initiate any strategies for purposes of addressing
2 the slow enrollment in 114?

3 A. Yes.

4 Q. What did you do?

5 A. To the best of my knowledge I would have
6 had the CRO contact the sites.

7 Q. Who is the CRO?

8 A. The clinical research organization and I
9 believe their name was RSI. They are our
10 go-between. I looked into a patient recruitment
11 firm. That's all I can recall.

12 Q. First you said you had the CRO contact
13 the investigation sites. You said they were the
14 go-between. Who was the CRO in this particular
15 trial?

16 A. RSI.

17 Q. That is the name of a company?

18 A. Yes.

19 Q. Do you know what that stands for, RSI?

20 A. Research Solutions, Incorporated.

21 Q. Have you used RSI as a CRO on clinical
22 trials at Abbott on more than one occasion?

23 A. I don't remember.

24 Q. Are you currently using them?

1 Q. Did you receive any feedback as a result
2 of that request?

3 A. I'm sure I did.

4 Q. What did you receive?

5 A. I don't remember.

6 Q. Do you have any further information as
7 you sit here today about what enrollment obstacles
8 were encountered in the 114 trial?

9 A. No.

10 Q. You made reference to the fact that you
11 tried to -- you looked into a patient recruitment
12 firm. What is a patient recruitment firm?

13 A. This is a vendor that comes up with
14 ideas, either through advertising, TV, radio, to
15 get the word out about the trial.

16 Q. How many patient recruitment firms did
17 you contact?

18 A. I only recall one and I don't even know
19 the name.

20 Q. Did you retain a patient recruitment
21 firm for the 114 trial?

22 A. I don't believe so.

23 Q. Why not?

24 A. I can't recall exactly, but they are

1 very expensive. So, I would speculate only.

2 Q. I don't want you to speculate.

3 A. Okay. Then no.

4 Q. Do you have any recollection as to why
5 you didn't retain one? Do you think part of it
6 might have had to do with the cost?

7 A. Probably.

8 MR. PHILLIPS: I would just caution the
9 witness not to speculate.

10 BY THE WITNESS:

11 A. Okay. I won't speculate. I don't know
12 why. I don't know why.

13 BY MR. DAVIS:

14 Q. Did you have an assistant on the 114
15 trial?

16 A. Yes.

17 Q. Who?

18 A. Kevin Heiser.

19 Q. What responsibilities did Mr. Heiser
20 have?

21 A. He was a CRA, clinical research
22 associate.

23 Q. What duties and responsibilities did he
24 have as clinical research associate with respect to

1 that trial?

2 A. As a clinical research associate he
3 would have been in contact with the CRO. He would
4 have been gathering numbers, getting information on
5 my direction, reviewing trip reports.

6 Q. Typically how many clinical trials do
7 you run as a project manager at any point in time?

8 A. Varies.

9 Q. At the time of this 114 trial were there
10 any other clinical trials that you were managing?

11 A. If I recall, 115.

12 Q. Which was a clinical trial that was in
13 the planning stage but not -- was never actually
14 undertaken by Abbott, correct?

15 A. Correct. The only trial that I
16 managed -- I was only managing one trial that was
17 actually ongoing, enrolling patients involved.
18 Then you could be doing other trials, preparation.

19 MR. DAVIS: Let's mark this as the next
20 exhibit, please, Exhibit 8.

21 (WHEREUPON, a certain document was

22 marked Collicott Deposition Exhibit

23 No. 8, for identification, as of

24 09-27-2006.)

1 BY MR. DAVIS:

2 Q. By the way, does Mr. Heiser still work

3 for Abbott?

4 A. I don't know. I don't know.

5 Q. You have what's been marked as

6 Exhibit 8. Have you seen this document before?

7 A. No.

8 Q. On the first page of this document,

9 there is a reference to Phase IIb studies.

10 A. Um-hmm, yes.

11 Q. You can see at the top of the document

12 it references "ABT-594 2001 Update." Do you see

13 that?

14 A. Yes.

15 Q. And the -- again, the 114 study was for

16 diabetic neuropathy, correct?

17 A. Correct.

18 Q. And you see that there are a series of

19 dates here for "Start (First Dose)," and "Last

20 Dose," "Subjects," "Sites," "EVR Sites," "EVR

21 Countries."

22 Do you see that?

23 A. Yes.

24 Q. And also "Comments"?

1 A. Yes.

2 Q. "Start (First Dose)," would that be the

3 date that you understand to be -- on which the

4 first patient would receive the first dose?

5 A. That would be the date --

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. The date the patient was randomized.

9 BY MR. DAVIS:

10 Q. The first patient?

11 A. Yes.

12 Q. And then the "End (Last Dose)" date,

13 would that be your understanding of the projected

14 date on which the last patient in the trial would

15 receive their last dose?

16 MR. PHILLIPS: Objection.

17 BY THE WITNESS:

18 A. Correct.

19 BY MR. DAVIS:

20 Q. And the subjects, was that the targeted

21 number of subjects called for in the trial

22 protocol?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 MR. PHILLIPS: Objection.

2 BY THE WITNESS:

3 A. Well, I didn't design the trial. So, I

4 don't know.

5 BY MR. DAVIS:

6 Q. Did you play any role in designing the

7 trial?

8 A. No.

9 Q. Did you --

10 A. I manage it.

11 Q. When you were administering, managing

12 the trial, did you understand that one of the

13 objectives of the trial was to try to understand

14 patient response to the three different dosing

15 levels?

16 MR. PHILLIPS: Objection.

17 BY THE WITNESS:

18 A. I don't know.

19 BY MR. DAVIS:

20 Q. Is that something you would have known

21 at the time?

22 MR. PHILLIPS: Objection.

23 BY THE WITNESS:

24 A. I don't know. Specifically I don't

1 BY THE WITNESS:

2 A. No.

3 BY MR. DAVIS:

4 Q. And then further down it says, one of
5 the bullet points says, "Define revised timeline
6 for development plan."

7 Do you see that?

8 A. Yes.

9 Q. Did you participate in coming up with a
10 revised timeline for the development plan for
11 ABT-594?

12 A. Not that I recall.

13 Q. Do you recall changing the timelines for
14 the 114 trial at any point in time during the
15 course of that trial?

16 MR. PHILLIPS: Objection.

17 BY THE WITNESS:

18 A. It's fuzzy. I really can't remember.

19 MR. DAVIS: Let's mark this as the next
20 exhibit, please, Exhibit 11.

21 (WHEREUPON, a certain document was

22 marked Collicott Deposition Exhibit

23 No. 11, for identification, as of

24 09-27-2006.)

1 BY MR. DAVIS:

2 Q. Ms. Collicott, you have what's been

3 marked as Exhibit 11 at your deposition. First let

4 me ask you: Have you seen this document before?

5 A. Yes.

6 Q. When did you last see this document?

7 A. Probably when I wrote it.

8 Q. That's your best recollection?

9 A. Hang on a second. Let me just read.

10 It's my best recollection.

11 Q. Did you in fact write the letter that's

12 attached to this e-mail?

13 A. Yes.

14 Q. And did you in fact send this e-mail to

15 Dr. Silber on or about August 31, 2000?

16 A. I can't confirm that. It certainly

17 appears that I did.

18 Q. Do you have any reason to doubt that you

19 sent it to him?

20 A. No.

21 Q. Now, why -- take a look at the letter

22 for a moment. Did you in fact send this letter out

23 to investigators in this trial?

24 A. I can't confirm that it went out. I

1 have no reason to doubt that it didn't.

2 Q. Do you recall extending the enrollment

3 period for 114 in the course of that trial?

4 A. Yes.

5 Q. Why was it that you extended the

6 enrollment period?

7 A. Because our enrollment numbers were

8 down. It's something we typically do.

9 Q. What would be -- what did you understand

10 to be the effect of not obtaining the targeted

11 number of subjects?

12 MR. PHILLIPS: Objection.

13 BY THE WITNESS:

14 A. From my standpoint that the effect of

15 not having the number of subjects would simply

16 reflect on my being able to manage the trial. How

17 it affects the trial itself, I don't know.

18 BY MR. DAVIS:

19 Q. Did you have any understanding as to

20 whether not -- not obtaining the targeted number of

21 subjects could affect the statistical significance

22 of the trial?

23 A. Not being a statistician, I couldn't

24 tell you.

1 Q. I'm not asking if you know for sure.

2 Did you have any general understanding
3 at this point in time, in mid-2000, that if you
4 didn't obtain 320 patients for that study that that
5 failure might affect the statistical significance
6 of the trial?

7 A. That I don't know.

8 Q. Did you have to request approval from
9 someone within Abbott in order to extend the
10 enrollment date for this trial?

11 A. I could not have decided that on my own.
12 But I don't know whose approval it would have
13 required.

14 Q. Do you recall any discussions with
15 anyone within Abbott concerning extending the
16 enrollment date of the trial?

17 A. I don't recall specifics of any
18 conversations.

19 Q. Do you recall generally any
20 conversations on that topic?

21 A. Other than that we were going to extend
22 it, no.

23 Q. Now, when you explained to people within
24 Abbott why you were extending it, what did you tell

1 them?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. I don't recall.

5 BY MR. DAVIS:

6 Q. Did you believe that it was desirable at

7 that point in time to extend the trial in order to

8 achieve the target number of subjects?

9 A. Yes.

10 Q. Did you believe at that point in time

11 that you would achieve the targeted number of

12 subjects if you did not extend the trial?

13 A. No.

14 MR. DAVIS: Let's mark this as the next

15 exhibit, please.

16 (WHEREUPON, a certain document was

17 marked Collicott Deposition Exhibit

18 No. 12, for identification, as of

19 09-27-2006.)

20 BY MR. DAVIS:

21 Q. Ms. Collicott, you have what's been

22 marked Exhibit 12. Do you recall seeing this

23 document before?

24 A. No.

1 Q. Who negotiated the original contracts?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. I don't know.

5 BY MR. DAVIS:

6 Q. Was that something that you expect you
7 would have done as clinical trial manager?

8 A. Again, every group is different and I
9 have worked in so many different groups. It could
10 have been something I did.

11 MR. DAVIS: Let's mark this as the next
12 exhibit, please.

13 (WHEREUPON, a certain document was
14 marked Collicott Deposition Exhibit
15 No. 15, for identification, as of
16 09-27-2006.)

17 THE WITNESS: Can I just interrupt a minute?

18 MR. DAVIS: Certainly.

19 THE WITNESS: I'm going to get cranky if I
20 don't get something to eat lunch. I don't mind a
21 working lunch. If we could start thinking about
22 food, I'd appreciate it.

23 MR. DAVIS: Your time here is just before
24 noon?

1 THE WITNESS: Yes.

2 MR. DAVIS: Could we stop at noon?

3 THE WITNESS: Sure. I don't mind if we sit

4 here and have a working lunch. That's great.

5 MR. PHILLIPS: I think we should take at least

6 a short break for lunch.

7 MR. DAVIS: That's fine. You are entitled to

8 be fed.

9 THE WITNESS: Thank you. Otherwise I am going

10 to get cranky.

11 MR. PHILLIPS: I'm sorry. Was this

12 Exhibit 15?

13 MR. DAVIS: It is Exhibit 15.

14 BY MR. DAVIS:

15 Q. You have Exhibit 15 in front of you,

16 Ms. Collicott. Again, do you recall seeing this

17 document?

18 A. I don't.

19 Q. You don't think you have ever seen this

20 document?

21 A. I don't think so.

22 Q. And this appears to be an October 2000

23 status report for the 594 project?

24 A. Yes.

1 Q. Under "Key Progress Gauges -
2 October Accomplishments," one of them states,
3 "Complete review of proposals from patient
4 recruitment firms for M99-114 and recommend steps
5 for 1Q01 implementation."

6 Do you see that?

7 A. Yes.

8 Q. The target date is 10/31 and then under
9 "Status" it says, "Complete - BBK chosen as best
10 candidate. Working with Abbott Public Affairs and
11 BBK to determine action plan."

12 A. Yes.

13 Q. Do you recall in fact that you worked up
14 an action plan with BBK to implement a patient
15 recruitment plan?

16 A. I don't know if it was a written action
17 plan. They would have made some recommendations to
18 me. What they were, I don't recall. I recall the
19 name BBK.

20 Q. Have you ever worked with BBK either
21 before or since this particular trial?

22 A. No.

23 Q. Have you used patient recruitment firms
24 before or since?

1 A. I don't recall.

2 Q. As you sit here you don't recall doing

3 so?

4 A. I don't recall whether I've actually

5 used one or just investigated it. I don't know.

6 MR. DAVIS: Let's mark this, please, as the

7 next exhibit, 16.

8 (WHEREUPON, a certain document was

9 marked Collicott Deposition Exhibit

10 No. 16, for identification, as of

11 09-27-2006.)

12 BY MR. DAVIS:

13 Q. Ms. Collicott, you have what's been

14 marked Exhibit 16. If you'd look at this document

15 for a moment and confirm for me, please, if you

16 can, that this is an e-mail and attachment that you

17 sent on or about October 9, 2000, regarding the 114

18 trial?

19 A. Yes.

20 Q. The people to whom you sent this e-mail,

21 who are they?

22 A. Susan Nunn was with data management;

23 Amy Hansen is with data management; Jim Thomas,

24 statistics; Ray Morales, an administrative

1 this trial --

2 A. Yes, I did.

3 Q. -- for purposes of this litigation?

4 A. Yes.

5 Q. And you did not find any?

6 A. I did not find a thing.

7 Q. If you look at the attachment to

8 Exhibit 16, there is -- there appears to be a

9 spreadsheet of some sort.

10 A. Yes.

11 Q. Is this a spreadsheet that you

12 maintained?

13 A. Either I maintained it or one of my

14 staff did.

15 Q. What was the purpose of this

16 spreadsheet?

17 A. Tracking enrollment.

18 Q. And you actually tracked enrollment data

19 on this spreadsheet, correct?

20 A. Yes.

21 Q. Down on the lower left corner of the

22 first page of the spreadsheet there is some

23 statistics there, "Screen Failure Rate." Do you

24 see that?

1 A. Yes.

2 Q. What is that?

3 A. That's patients who failed to be

4 randomized.

5 Q. The "Early Termination Rate." Do you

6 see that?

7 A. Yes.

8 Q. What's that?

9 A. The patient who fails to complete the

10 study once randomized.

11 Q. Would early termination affect the

12 enrollment in the study?

13 A. No.

14 Q. Was there anything about the early

15 termination rate in this study that ever concerned

16 you?

17 A. No.

18 Q. Not at any point in time?

19 A. No.

20 Q. Did you regard the early termination

21 rate in this study to be unusual in any way?

22 A. No.

23 Q. Then there is a "Completion Rate." What

24 is that?

1 A. Subjects who actually completed all

2 visits.

3 Q. So, a patient who enrolled in the study

4 but then terminated early was still considered to

5 be an enrolled patient for purposes of reaching the

6 320 patient --

7 A. Yes.

8 Q. -- target?

9 A. Yes.

10 Q. Some of the -- if you take a look again

11 at Exhibit 10 for a moment, which is the

12 August 2000 project status report. Do you have

13 that?

14 A. Okay, yes.

15 Q. Again, the first bullet point under "Key

16 Progress Gauges - August Accomplishments," it

17 says, "Complete assessment of M99-114 premature

18 discontinuations and recommend enrollment action

19 plan."

20 Do you see that?

21 A. Yes.

22 Q. Are premature discontinuations the same

23 as premature terminations?

24 A. Yes.

1 Q. Why was it at that point in time, to
2 your knowledge, that Abbott was concerned about the
3 or thought that it was necessary to come up with an
4 enrollment action plan or to assess the premature
5 discontinuations in that context?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. I'm not sure why Abbott -- I don't see a
9 connection between the two. Enrollment action
10 plans is very typical.

11 BY MR. DAVIS:

12 Q. And then there is reference there to
13 assessment of the premature discontinuations. What
14 concern or what potential concern might Abbott have
15 regarding the premature discontinuations at that
16 point in time?

17 MR. PHILLIPS: Objection.

18 BY THE WITNESS:

19 A. That would not have been my concern as a
20 trial manager. Why they would have done that, I
21 don't know.

22 MR. DAVIS: Let's mark this as the next
23 exhibit, please, 17.

24 (WHEREUPON, a certain document was

1 A. I don't know.

2 Q. Do you know why it was not deemed to be
3 a viable option as of November 2000 to hire a
4 recruitment firm to increase enrollment in the 114
5 study? Do you know why it was not -- why it was
6 considered to be not a viable option?

7 A. At this point in time I would have to
8 speculate.

9 Q. I don't want you to speculate.

10 A. No. I don't recall. It's just been too
11 long.

12 Q. Are you aware of any reason why Abbott
13 could not retain a recruitment firm at that point
14 in time?

15 A. No, I don't know.

16 Q. Do you recall being told that you could
17 not retain a recruitment firm?

18 A. No, I don't recall that.

19 MR. DAVIS: Let's mark this as Exhibit 18,
20 please.

21 (WHEREUPON, a certain document was
22 marked Collicott Deposition Exhibit

23 No. 18, for identification, as of
24 09-27-2006.)

1 BY MR. DAVIS:

2 Q. You have what's been marked as

3 Exhibit 18, Ms. Collicott. Would you take a moment

4 to look at that document and tell me if you have

5 seen it before, please.

6 A. I don't recall whether I've seen it. I

7 don't recall.

8 Q. In the course of your work at Abbott, do

9 you recall ever being consulted by anyone at Abbott

10 for purposes of obtaining information to provide to

11 John Hancock regarding the status of 594?

12 A. No.

13 Q. Were you ever asked to provide any

14 information to John Hancock on the status of 594?

15 A. No.

16 Q. If you'd look at this document, please,

17 Exhibit 18, I note that all of the pages of this

18 document are labeled page 8. But if you -- it's

19 apparently a very long page. But if you look at

20 the one that's Bates numbered that ends in 4606.UR.

21 Do you see that?

22 A. Got it.

23 Q. There is a section titled -- under

24 "Product/Development Background" there is a

1 subsection titled "Clinical Studies."

2 Do you see that?

3 A. Yes.

4 Q. And in the first paragraph there is a

5 reference to Phase IIa studies with ABT-594 SEC

6 formulation?

7 A. Yes.

8 Q. What is SEC formulation?

9 A. Soft elastic capsule.

10 Q. It says first in that paragraph that

11 "ABT-594 was generally well tolerated in these

12 studies."

13 Do you see that?

14 A. Yes.

15 Q. Is that consistent with your

16 recollection?

17 A. Yes.

18 Q. Now, the next paragraph says, "A

19 Phase IIb study for neuropathic pain at higher,

20 titrated doses of ABT-594 began in April 2000 and

21 ends in June 2001."

22 Do you see that?

23 A. Yes.

24 Q. That's reference to the 114 study, is

1 says, "M99-114 Enrollment Cutoff, March 02, 2001."

2 Do you see that?

3 A. Yes.

4 Q. As of at least the date of that meeting

5 was that the expected enrollment cutoff for the 114

6 trial?

7 A. Yes.

8 MR. DAVIS: Mark this as Exhibit 22.

9 (WHEREUPON, a certain document was

10 marked Collicott Deposition Exhibit

11 No. 22, for identification, as of

12 09-27-2006.)

13 BY MR. DAVIS:

14 Q. Ms. Collicott, you have Exhibit 22,

15 which on its face purports to be a December 2000

16 ABT-594 project status report.

17 Have you seen this document before?

18 A. No.

19 Q. First item listed under "Key

20 Issues/Decisions/Events," says, "Area. Venture.

21 Closing of enrollment on M99-114 as of January 5,

22 2001."

23 Do you see that?

24 A. Yes.

1 Q. Did you participate in that decision?

2 A. No, not that I can recall.

3 Q. Who made that decision?

4 A. I don't recall who -- who did it.

5 Q. Someone above you?

6 A. Yes.

7 Q. Was Mr. McCarthy a participant in that

8 decision to your knowledge?

9 MR. PHILLIPS: Objection.

10 BY THE WITNESS:

11 A. I don't know.

12 BY MR. DAVIS:

13 Q. Was the decision communicated to you at
14 some point in time?

15 A. Yes.

16 Q. By who?

17 A. I'm not sure.

18 Q. Was the reasoning behind the decision
19 explained to you?

20 A. I don't recall what the reasoning was.

21 Q. Do you have any recollection of any
22 discussions with anyone at Abbott about the
23 decision to close the enrollment of the 114 trial
24 as of January 5, 2001?

1 A. Other than the fact that we were going

2 to do it, no. I don't recall any conversations.

3 Q. Did the decision to close the enrollment
4 as of January 5, 2001 constitute a change to the --
5 the clinical trial plan?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. I'm trying to think. Trial plans change
9 and are revised all the time. So...

10 I can't -- I can't remember.

11 BY MR. DAVIS:

12 Q. I think earlier today, Ms. Collicott, we
13 looked at some correspondence that you sent out to
14 the investigative sites that you were actually
15 extending the enrollment date?

16 A. Right.

17 Q. And then you decided to thereafter --
18 Abbott decided to cut the enrollment date back
19 again to January 5, 2001, correct?

20 MR. PHILLIPS: Objection.

21 BY THE WITNESS:

22 A. Appears to be, yes.

23 BY MR. DAVIS:

24 Q. That's consistent with your

1 investigators on the trial?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. I believe it was, yes.

5 BY MR. DAVIS:

6 Q. As we sit here today you have no further
7 recollection or knowledge regarding the reasoning
8 behind or the reasons behind the decision to close
9 enrollment on that trial on January 5, 2001?

10 A. No. I'd be speculating.

11 MR. DAVIS: Let's mark this, please, as

12 Exhibit 23.

13 (WHEREUPON, a certain document was

14 marked Collicott Deposition Exhibit

15 No. 23, for identification, as of

16 09-27-2006.)

17 BY MR. DAVIS:

18 Q. Ms. Collicott, you have Exhibit 23. Let
19 me ask you if you have seen this document before.

20 A. No, I have not.

21 Q. Have you ever seen within Abbott a list
22 of top issues with respect to particular compounds?

23 A. No.

24 Q. About a third of the way down this

1 page do you see a reference to ABT-594 and it
2 says, "Closing of enrollment on M99-114 as of
3 January 5, 2001"?

4 Do you see that?

5 A. Yes, I do.

6 Q. And then it goes on to say, "It was
7 agreed in December to close enrollment into
8 M99-114, our Painful Diabetic Neuropathy trial, as
9 of January 5, 2001. This is two months ahead of
10 our most recent estimate of March 5, 2001 and will
11 include less than our original target of 320
12 patients."

13 Do you see that?

14 A. Yes.

15 Q. Is that consistent with your
16 understanding of what was happening at the time?

17 A. Yes.

18 Q. Did you understand as of December 2000
19 that if the enrollment was closed in the 114 trial
20 as of January 5, 2001, that it meant that the
21 number of subjects in the trial would likely be
22 less than 320?

23 A. That one I can't be sure of.

24 Q. Well, you see here it says the trial

1 Who had a desire to evaluate the outcome
2 of the study?

3 MR. PHILLIPS: Objection.

4 BY THE WITNESS:

5 A. I don't know.

6 BY MR. DAVIS:

7 Q. Was that ever explained to you?

8 A. No. I just managed the study.

9 Q. Then it says, also says, "And an
10 assessment of the statistical power of the study."

11 Do you recall any discussions within
12 Abbott regarding what effect closing enrollment on
13 January 5, 2001 would have on the statistical power
14 of the 114 study?

15 A. I wouldn't have had the knowledge of
16 that.

17 MR. DAVIS: Let's mark this, please, as the
18 next exhibit. We're up to Exhibit 24.

19 (WHEREUPON, a certain document was
20 marked Collicott Deposition Exhibit
21 No. 24, for identification, as of
22 09-27-2006.)

23 BY MR. DAVIS:

24 Q. Ms. Collicott, you have Exhibit 24. If

1 you'd take a moment to look at it and then tell me

2 if this is a copy of some e-mail that you exchanged

3 with --

4 A. Biarnesen.

5 Q. -- Biarnesen.

6 A. I'm not going to go with you to your

7 next deposition to help.

8 Q. Back in late 2000.

9 MR. PHILLIPS: You have to have phonetics.

10 MR. DAVIS: Hold on. I am going to do it.

11 Biarnesen.

12 MR. PHILLIPS: I'm sorry. Do you have the

13 question in mind?

14 MR. DAVIS: I will repeat the question.

15 BY MR. DAVIS:

16 Q. The question is: Is this a copy of some

17 e-mail communications that you had with

18 Mr. Biarnesen back in late 2000?

19 A. Okay.

20 Okay.

21 Q. Is this a copy of e-mail communications

22 that you had with Mr. Biarnesen back in late 2000?

23 A. Yes.

24 Q. Now, it starts with an e-mail from you

1 Mr. Biarnesen to you on December 6. Do you see
2 that?

3 A. Um-hmm.

4 Q. And he says, "How about 260 for the
5 randomization goal? We already have 251."

6 Do you see that?

7 A. Yes.

8 Q. Do you recall having communications with
9 Mr. Biarnesen about what would be perhaps a revised
10 target or goal for the trial?

11 A. No. I don't.

12 Q. Then you wrote back to Mr. Biarnesen, if
13 I am reading this, "Welllllllllll," with many Ls?

14 A. Yes.

15 Q. "Okay. I just have a feeling the bottom
16 is going to drop out of this thing in the next few
17 weeks and we'd be lucky to randomize 1-2/week. (Oh
18 God - I'm turning into an Eeyore!!)"

19 Did I read that correctly?

20 A. Yes, you did certainly.

21 Q. You felt that the bottom was going to
22 drop out of this thing in the next few weeks. What
23 did you think that the bottom might drop out of?

24 A. Enrollment.

1 Q. You thought that enrollment would not
2 improve, is that fair to say?

3 A. Right. Based on the date of the e-mail,
4 with the holidays coming up, we generally see
5 enrollment bottoming out.

6 Q. Is it fair to say that at least as of
7 the date of this e-mail you thought it unlikely
8 that this study would reach 320 subjects?

9 MR. PHILLIPS: Objection.

10 BY THE WITNESS:

11 A. I'm not sure that's what I was saying.

12 BY MR. DAVIS:

13 Q. Is that what -- when you were saying you
14 thought the bottom was going to drop out, did you
15 mean that you thought you were going to hit 320
16 subjects?

17 MR. PHILLIPS: Objection.

18 BY THE WITNESS:

19 A. No, it just was that the -- in context
20 of that date, we weren't going to have a lot of
21 enrollment in the next few weeks because of the
22 holidays.

23 BY MR. DAVIS:

24 Q. Did you think it would pick up right

1 after the holidays?

2 A. I don't know what I thought at that

3 time.

4 Q. Why did you say "I'm turning into an

5 Eeyore"?

6 A. Eeyore always says, "The sky is falling.

7 Oh, woe is me."

8 Q. Did you think the sky was falling on

9 this particular clinical trial at that time?

10 A. No, just enrollment was going to bottom
11 out because of the holidays, something we see all
12 the time.

13 MR. DAVIS: Let's mark this as the next
14 exhibit, please. We're up to Exhibit 25.

15 (WHEREUPON, a certain document was
16 marked Collicott Deposition Exhibit
17 No. 25, for identification, as of
18 09-27-2006.)

19 BY MR. DAVIS:

20 Q. Ms. Collicott, you have a copy of what's
21 been marked as Exhibit 25. Please take a look at
22 it for a moment and tell me if you have seen this
23 document before.

24 A. Yes, I have.

1 Q. When did you last see this document?

2 A. Yesterday.

3 Q. Now, this is a copy of an e-mail that

4 you sent to the various people listed on the front

5 of the e-mail, correct?

6 A. Yes.

7 Q. Did you actually send it on or about

8 December 14, 2000?

9 A. I would say so.

10 Q. Okay. How did you select these

11 particular people to receive this e-mail?

12 A. These are members of the team.

13 Q. Is everyone here a member of the team?

14 A. I couldn't -- I'd have to read the

15 names. Some of the names, again, I don't recall

16 what their role was.

17 Q. Did you maintain a distribution list on

18 your e-mail at that point in time that had all of

19 the members of the team on the distribution list?

20 A. I wasn't good with just distribution

21 lists. I generally just put names in.

22 Q. Wow.

23 A. I know.

24 Q. You really ought to get the hang of

1 those distribution lists.

2 A. I know.

3 Q. You say in the e-mail --

4 A. I still don't get them.

5 Q. -- "A decision has been made to stop

6 enrollment for study M99-114 on January 5, '01.

7 Subjects may be randomized up through that date. I

8 have attached a copy of the letter that is being

9 Fed Ex'd to all sites today. If you have any

10 questions, please don't hesitate to contact me."

11 Did I read that correctly?

12 A. Yes, you have.

13 Q. Who drafted the letter that's attached?

14 A. I drafted it.

15 Q. Where did you get the information

16 contained in the letter?

17 A. I couldn't tell you exactly who I got it

18 from.

19 Q. Do you recall generally who you got it

20 from?

21 A. Someone in the department higher than

22 me.

23 Q. You can't be any more specific than

24 that?

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1 A. It could be Bruce, it could be Chris, it
2 could be somebody in statistics because I don't
3 have a -- I had no knowledge of the powering and
4 how those things are determined. So I would have
5 received that information from someone, but I just
6 don't know who.

7 Q. Well, is the information contained in
8 the letter accurate?

9 MR. PHILLIPS: Objection.

10 BY MR. DAVIS:

11 Q. To the best of your knowledge.

12 A. Well, since I don't understand the
13 powering portion of it and that's not part of what
14 I do, I can't tell you if that was accurate or not
15 from a statistical standpoint.

16 Q. Did you believe it to be accurate at
17 that point in time?

18 MR. PHILLIPS: Objection.

19 BY THE WITNESS:

20 A. Yes.

21 BY MR. DAVIS:

22 Q. You wouldn't send out a letter to
23 investigators on a clinical trial containing what
24 you thought was inaccurate information, correct?

1 A. I would have trusted the judgment of the
2 people that provided me the information.

3 Q. It says --

4 A. Because there is -- go ahead.

5 Q. I'm sorry. I did not mean to cut you
6 off.

7 A. No, I'm done.

8 Q. It says in the second paragraph of the
9 letter -- the first paragraph says, "We have
10 decided to end enrollment in the above referenced
11 study on January 5, 2001."

12 It goes on to say, "As specified in the
13 protocol, 80 percent power would have been achieved
14 with the randomization of 320 subjects, assuming
15 there were no premature terminations."

16 Do you see that?

17 A. Yes.

18 Q. What did you mean by that?

19 A. That is a statistical sentence that
20 would have been provided by statistics.

21 Q. Did you understand the sentence at the
22 time you wrote the letter?

23 A. I would have had a general
24 understanding, but I would not have known

1 specifics. Again, when it comes to statistics or
2 the protocol, that information is all given to me
3 by that group.

4 Q. What did you refer to -- what did you
5 mean by 80 percent power?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. It's a statistical term.

9 BY MR. DAVIS:

10 Q. Do you have any further -- can you
11 relate to me any further knowledge or information
12 you have regarding the meaning of that term as you
13 used it in this letter that you drafted?

14 MR. PHILLIPS: Objection.

15 BY THE WITNESS:

16 A. I'm -- I can't.

17 BY MR. DAVIS:

18 Q. How did you understand -- strike that.

19 To your knowledge, how could the
20 premature termination rate affect the power of the
21 study?

22 MR. PHILLIPS: Objection.

23 BY THE WITNESS:

24 A. I don't know.

1 BY MR. DAVIS:

2 Q. Could the -- the next sentence
3 says, "Our current premature termination rate,
4 however, will result in less than 80 percent power
5 even if we were to reach our enrollment goal."

6 Do you see that?

7 A. Yes, I see it.

8 Q. Is it your understanding at this time
9 that the premature termination rate was going to
10 affect the statistical power of the study?

11 MR. PHILLIPS: Objection.

12 BY THE WITNESS:

13 A. Again, not being a statistician, I don't
14 know how that affects the power of the study.

15 BY MR. DAVIS:

16 Q. My question is slightly different,
17 though.

18 A. Okay.

19 Q. My question is did you understand at the
20 time that you drafted this letter that the
21 premature termination rate on the 114 study was
22 going to have some impact on the statistical power
23 of the study?

24 A. Based on what the letter says, yes.

1 Q. Do you know --

2 A. Do I have an understanding of how it

3 affects? No.

4 Q. My next question is: Did you understand
5 that it was going to have an adverse impact on the
6 statistical power of the study?

7 A. No.

8 MR. PHILLIPS: Objection.

9 BY MR. DAVIS:

10 Q. Did you think it was going to enhance
11 the statistical power of the study?

12 A. I didn't know. I didn't know.

13 Q. You go on to say, "After reviewing
14 possible outcomes with our statisticians."
15 Did you review possible outcomes with
16 statisticians?

17 A. Not me personally.

18 Q. It says, "We concluded that ending
19 enrollment prior to reaching our goal of 320
20 subjects will not meaningfully change our ability
21 to interpret the results of this study."

22 What did you mean by that?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 investigators on the 114 study?

2 A. Whether it was this letter, we would

3 have had to notify investigators to stop

4 enrollment. Whether it was this letter that went

5 out, I don't know.

6 MR. DAVIS: Let's mark this as the next

7 exhibit, please.

8 (WHEREUPON, a certain document was

9 marked Collicott Deposition Exhibit

10 No. 26, for identification, as of

11 09-27-2006.)

12 BY MR. DAVIS:

13 Q. Ms. Collicott, I want to show this one

14 to you. This is Exhibit 26. Is this an e-mail

15 attachment that you sent on or about December 12 --

16 December 14, 2000?

17 A. Yes.

18 Q. And who is Mr. Schanzenbach?

19 A. He was the project manager for our CRO.

20 Q. I'm sorry. He was the project manager

21 for CRO?

22 A. For the CRO.

23 Q. This is -- I think you mentioned him

24 earlier today, is that correct?

1 A. Well, I'm sure Bruce McCarthy probably
2 had input into that. Statisticians would have had
3 input into it. Chris Silber.

4 Q. Anyone else that you can think of?

5 A. Not offhand.

6 MR. DAVIS: Mark this as the next exhibit. I

7 think we are up to 27.

8 (WHEREUPON, a certain document was

9 marked Collicott Deposition Exhibit

10 No. 27, for identification, as of

11 09-27-2006.)

12 BY MR. DAVIS:

13 Q. Ms. Collicott, you have what's been

14 marked Exhibit 27. It appears to be on its face a

15 January 2001 ABT-594 project status report.

16 Have you seen this document before?

17 A. I don't recall seeing this.

18 Q. It says in the very first bullet point

19 under "Monthly Highlights," "Enrollment closed for

20 our Phase IIb Painful Diabetic Polyneuropathy trial

21 (M99-114), with total enrollment reaching 269. The

22 Last patient will complete the study at the end of

23 February and the results will be available at the

24 end of May."

1 Do you see that?

2 A. Yes.

3 Q. Is that your understanding of the final

4 enrollment in that study was 269?

5 A. I don't recall what the final enrollment

6 was. I -- off the top of my head I don't know.

7 Q. After enrollment was ended -- strike

8 that.

9 Did in fact enrollment end in the 114

10 study as of January 5, 2001?

11 A. To the best of my knowledge it did, but

12 sometimes there are stragglers and I couldn't -- I

13 couldn't attest to the fact that somebody didn't

14 enroll after that date.

15 Q. Did it end on or about that date?

16 A. I'd say yes.

17 Q. Did it reach 320 subjects?

18 A. No.

19 Q. After enrollment was ended, did you have

20 any expectation that the total number of subjects

21 enrolled in that trial would reach 320?

22 A. No.

23 Q. There is a reference under "Key Progress

24 Gauges" to "Prepare study closeout timelines."

1 MR. DAVIS: Let's mark this as the next
2 exhibit, please.

3 (WHEREUPON, a certain document was
4 marked Collicott Deposition Exhibit
5 No. 28, for identification, as of
6 09-27-2006.)

7 BY MR. DAVIS:

8 Q. Ms. Collicott, you have Exhibit 28 in
9 front of you. Is this an e-mail that you sent to
10 Mr. Schanzenbach?

11 A. Yes.

12 Q. On January 8, 2001?

13 A. Yes.

14 Q. It says -- by the way, what is a query
15 tracking report?

16 A. It would track the resolution of all
17 data queries.

18 Q. What's a data queries?

19 A. When the case report forms come in, they
20 are reviewed for completeness and accuracy. If
21 there is any questions, a data query is generated
22 in which the monitor goes back to the site to get
23 clarification. An addendum may or may not be
24 written to the case report form.

1 Q. Is this part of the process of cleaning

2 up the data?

3 A. Yes.

4 Q. Who maintains the tracking reports?

5 A. It could be a number of people. I could

6 maintain a report. Schanzenbach probably -- would

7 have maintained a report. Data management would

8 have maintained a report. Whose report this is,

9 I'm not sure.

10 Q. This has attached to it a tracking

11 report as of 8 January '01, correct?

12 A. Yes.

13 Q. Was the data accurate as of that date as

14 far as you know?

15 A. The data included in this tracking

16 report?

17 Q. Yes.

18 A. Let me just look at it quickly. I can't

19 be certain, but it would appear to be correct.

20 Q. The tracking report as of January 8,

21 '01, notes that the subjects enrolled to date are

22 269.

23 Again, to your knowledge, is that the

24 final total of subjects that were enrolled in this

1 particular study, keeping in mind that this is

2 January 8, 2001?

3 A. Yes.

4 Q. Up at the top your e-mail to

5 Mr. Schanzenbach states that, "FYI - query tracking

6 report. This becomes quite the big deal at this

7 stage of the game."

8 What did you mean?

9 A. As with any trial, getting the database

10 clean in order to break the blind and move forward

11 becomes a very hot topic at this time. We have to

12 keep after investigators to get them to sign off on

13 addendums, to answer our questions. This is a very

14 typical time in which we need to push.

15 MR. DAVIS: Let's mark this as the next

16 exhibit, which brings us up to Exhibit 29.

17 (WHEREUPON, a certain document was

18 marked Collicott Deposition Exhibit

19 No. 29, for identification, as of

20 09-27-2006.)

21 BY MR. DAVIS:

22 Q. Ms. Collicott, you have Exhibit 29 in

23 front of you. Let me ask you if this is an e-mail

24 attachment that you sent out on or around

1 January 16, 2001?

2 A. It looks to be.

3 Q. Were you generally responsible for

4 preparing agendas for meetings?

5 A. I don't recall if it was me or one of my

6 staff that actually did the agendas.

7 Q. Attached to the agenda is an

8 investigator list. Do you see that?

9 A. Yes.

10 Q. I don't think we have seen a version of

11 this before.

12 And then attached to that is also

13 another document titled "M99-114 Early

14 Terminations."

15 Do you see that?

16 A. Yes.

17 Q. Is that a database that you or someone

18 else at Abbott maintained?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. I'm not sure who maintained this.

22 BY MR. DAVIS:

23 Q. Why was it that someone maintained some

24 sort of spreadsheet of early terminations in this

1 would not -- is something I would have expected to
2 see.

3 Does that answer your question?

4 Q. I think my question was do you have any
5 knowledge of the significance of the early
6 termination rate?

7 A. No.

8 Q. On the -- going back to the investigator
9 list, can you see in the lower left-hand corner of
10 the first page of the spreadsheet references to
11 screen failure rate, early termination rate,
12 et cetera? Do you see that?

13 A. Yes.

14 Q. Again, the early termination rate shows
15 at 46 percent. Do you see that?

16 A. Yes.

17 Q. Is that 46 percent of the total number
18 of subjects enrolled in the trial?

19 A. Yes.

20 Q. Was there anything about that rate that
21 you thought was unusual or significant as of
22 January 2001?

23 A. No.

24 Q. Do you think that that was a high early

1 termination rate?

2 MR. PHILLIPS: Objection.

3 BY THE WITNESS:

4 A. Again, it depends on the trial. It
5 depends on your patient population. If you have
6 old, sick people, it's going to be different than
7 if you have young, healthy people.

8 BY MR. DAVIS:

9 Q. Was that a higher early termination rate
10 than you were used to seeing in clinical trials
11 that you conducted?

12 A. I honestly can't remember what early
13 termination rates have been in my trials.

14 Q. Do you recall thinking at the time that
15 that early termination rate was higher than you
16 typically had seen in the past?

17 A. I don't recall that.

18 Q. Anything about the early termination
19 rate for this particular trial that concerned you
20 at any time?

21 A. No.

22 MR. DAVIS: Let's mark this, please, as the
23 next exhibit. We are up to 30.

24 (WHEREUPON, a certain document was

1 marked Collicott Deposition Exhibit

2 No. 30, for identification, as of

3 09-27-2006.)

4 BY MR. DAVIS:

5 Q. Ms. Collicott, you have I think what's

6 been marked Exhibit 30. Look at that document,

7 please, and tell me if that is a copy of an e-mail

8 that you sent out on or about January 18, 2001.

9 A. I'm just going to read it quickly.

10 Yes.

11 Q. Who is D. Sharma or Deepak Sharma?

12 A. I have no idea.

13 Q. You state in your e-mail to I think it's

14 Mr. Sharma that "I am the Clinical Project Manager

15 in the Analgesia Venture and can answer your

16 questions about ABT-594. We are currently in

17 Phase II of development having just completed a

18 study for neuropathic pain."

19 Is that statement correct?

20 A. Yes.

21 Q. It says, "There is the potential we may

22 do an OA trial yet this year."

23 Is that a reference to the 115 trial?

24 A. Yes.

1 Q. "Studies are being conducted in the US
2 only at the present time. If you have additional
3 questions, please don't hesitate to e-mail me."

4 Do you recall when it was that the
5 decision was made within Abbott not to proceed with
6 the 115 trial?

7 A. I don't remember what the decision was
8 or why.

9 Q. You recall that Abbott did not undertake
10 the 115 trial?

11 A. Yes.

12 Q. Do you recall when it was that you
13 learned that Abbott was not going to proceed with
14 that trial?

15 A. I don't remember.

16 MR. DAVIS: Let's mark this as the next
17 exhibit, please.

18 (WHEREUPON, a certain document was

19 marked Collicott Deposition Exhibit

20 No. 31, for identification, as of

21 09-27-2006.)

22 BY MR. DAVIS:

23 Q. Ms. Collicott, you have Exhibit 31. Let
24 me ask you if you have seen this document before.

1 A. I don't recall seeing this.

2 MR. PHILLIPS: Ms. Collicott, make sure you
3 have a chance to look through it. I don't want you
4 to --

5 THE WITNESS: Oh, I'm sorry.

6 MR. PHILLIPS: Just look through it. I'm not
7 suggesting one way or the other, but just make
8 sure.

9 THE WITNESS: But -- okay.

10 BY THE WITNESS:

11 A. I don't recall whether I have seen this
12 or not.

13 BY MR. DAVIS:

14 Q. This is a descriptive memorandum dated
15 February 2001.

16 I just want to direct your attention to
17 the page that is numbered in the lower right-hand
18 corner ends in 6082.

19 MR. PHILLIPS: I notice it's paginated
20 incorrectly.

21 MR. DAVIS: One change was made.

22 MR. PHILLIPS: At least one correction.

23 BY THE WITNESS:

24 A. Okay. I have it.

1 BY MR. DAVIS:

2 Q. You see that there is a section again
3 entitled "Product/Development Background" and then
4 a subsection entitled "Clinical Trials"?

5 A. Yes.

6 Q. It says, "A Phase IIb study for
7 neuropathic pain at higher, titrated doses of
8 ABT-594 began in April 2000 and ends in June 2001."

9 Do you see that?

10 A. Yes.

11 Q. It goes on to say, "A total of 320
12 patients is anticipated to be included in the
13 study."

14 Do you see that?

15 A. Yes.

16 Q. You did not anticipate as of
17 February 2001 that 320 -- a total of 320 patients
18 would be included in the 114 study. Correct?

19 A. Correct.

20 Q. You knew at least as of February 2001
21 that that study already -- enrollment in that study
22 had already ended at somewhere in the vicinity of
23 260 to 270 patients, correct?

24 A. Yes.

1 MR. PHILLIPS: Objection.

2 BY THE WITNESS:

3 A. I can't state for certain that he was

4 aware.

5 BY MR. DAVIS:

6 Q. Is it your belief that he was aware?

7 MR. PHILLIPS: Objection.

8 BY THE WITNESS:

9 A. I believe he was aware.

10 BY MR. DAVIS:

11 Q. Is it something that you think you

12 informed him of prior to February 2001?

13 A. He would have known that, yes.

14 Q. How about Dr. Silber, do you think

15 Dr. Silber would have known prior to February 2001

16 that the 114 study had ended with less than 320

17 patients?

18 A. That one I couldn't tell you for sure.

19 MR. DAVIS: Let's mark this, please, as the

20 next exhibit, 32, please.

21 (WHEREUPON, a certain document was

22 marked Collicott Deposition Exhibit

23 No. 32, for identification, as of

24 09-27-2006.)

1 BY MR. DAVIS:

2 Q. We have marked this as Exhibit 32,
3 correct?

4 A. Correct.

5 Q. Ms. Collicott, you have in front of you
6 Exhibit 32, which appears to be a slide
7 presentation for project review for ABT-089 and
8 ABT-594 and dated February 2, 2001.

9 Let me ask you first. Did you
10 participate -- have you seen this document before?

11 A. I don't recall seeing this document
12 before.

13 Q. Did you participate in any project
14 review for ABT-594 on February 2, 2001?

15 A. I don't remember.

16 Q. Do you have any recollection of
17 participating in any sitdown meeting with
18 Dr. Leiden or other senior management of Abbott at
19 that time?

20 A. I would not have met with Dr. Leiden.

21 Q. Have you ever met Dr. Leiden?

22 A. I think I have met him once but not as
23 part of any meeting.

24 Q. Did your meeting with Dr. Leiden have

1 anything to do with ABT-594?

2 A. I'm sorry?

3 Q. Did your meeting with Dr. Leiden have

4 anything to do with ABT-594?

5 A. No, not at all.

6 Q. To your knowledge --

7 A. I could tell you what he looked like.

8 That's about it.

9 Q. Yeah, I have seen him on the web, too.

10 A. Okay.

11 Q. Did you, to your knowledge, participate

12 in any way in the creation of this slide

13 presentation?

14 A. I don't remember.

15 Q. Do you recall assisting Dr. McCarthy in

16 that time frame with the preparation of a slide

17 presentation for Abbott's senior management?

18 A. I don't recall. I generally would not

19 have done that.

20 Q. Would you look, please -- it's about, I

21 don't know, four-fifths of the way into this

22 document. It's the page that ends in 02433.

23 A. Yes.

24 Q. Do you have that slide in front of you?

1 A. Yes.

2 Q. You see it's a slide that is titled

3 "M99-114 Status." That is a reference to your

4 clinical trial, right?

5 A. Yes.

6 Q. And it says, "Enrollment - Ended 1/5/01

7 at 269 subjects."

8 Do you see that?

9 A. Yes.

10 Q. Is that consistent with your

11 recollection?

12 A. Yes.

13 Q. It then says, "Pre-specified power not

14 reached."

15 What's your understanding as to the

16 meaning of that sentence?

17 MR. PHILLIPS: Objection.

18 BY THE WITNESS:

19 A. Since I didn't make this slide, I don't

20 really know. I don't really know.

21 BY MR. DAVIS:

22 Q. Do you know what a pre-specified power

23 is?

24 MR. PHILLIPS: Objection.

1 BY THE WITNESS:

2 A. I --

3 MR. PHILLIPS: I'm sorry.

4 THE WITNESS: That's all right.

5 BY THE WITNESS:

6 A. If there was a power specified in the

7 protocol. That may be what it means.

8 BY MR. DAVIS:

9 Q. Do you recall any discussions within

10 Abbott that by ending enrollment for the 114 study

11 early, that the statistical power of the study had

12 been affected or compromised in any way?

13 A. I don't remember any conversations like

14 that. But I'm not a statistician so I would not

15 have been included in anything like that.

16 MR. DAVIS: Why don't we take a two- or

17 three-minute break if it's all right.

18 MR. PHILLIPS: Sure.

19 (WHEREUPON, a recess was had

20 from 1:34 to 1:42 p.m.)

21 BY MR. DAVIS:

22 Q. Ms. Collicott, back on the record.

23 May I ask you to look again briefly at

24 Exhibit 29, which is this e-mail with some of the

1 spreadsheets attached.

2 A. Yes.

3 Q. First, am I correct that the documents

4 that appear to be spreadsheets that are attached to

5 the agenda are in fact spreadsheets?

6 A. Yes.

7 Q. They are maintained by someone at

8 Abbott, as far as you know?

9 A. It would either have been at Abbott or

10 with the CRO.

11 Q. And provided to Abbott?

12 A. Yes.

13 Q. Again, we have been talking I think

14 earlier about adverse events and also early

15 terminations. Are those linked in some way?

16 A. They can be.

17 Q. So, for example, if you look at the list

18 of early terminations for the 114 study, it gives

19 "Reason For Termination." Do you see that column?

20 MR. PHILLIPS: I'm sorry. What page are you

21 on?

22 BY THE WITNESS:

23 A. Yes.

24 MR. DAVIS: I'm looking at page 2697.

1 MR. PHILLIPS: Thank you.

2 BY MR. DAVIS:

3 Q. You see there is reason for termination

4 given?

5 A. Yes.

6 Q. Is it fair to say that at least the

7 early terminations that are listed in this portion

8 of the chart are attributable to some sort of

9 adverse event?

10 A. If it says AE in front of it. So,

11 reason for termination AE would be an AE.

12 Q. You would agree with me, looking at that

13 page, the one that ends 2697, and the following

14 page, 2698, that the majority of early terminations

15 on this trial were attributable to adverse events?

16 A. It appears to be, yes. And that's not

17 unusual.

18 Q. At some point in time were you called

19 upon to put together a report, a final report with

20 respect to the 114 trial?

21 A. A final report is written, but not by

22 me.

23 Q. Do you participate in the preparation of

24 the final report?

1 Q. Did anyone in the course of the 114
2 trial ever notify you of any significant changes in
3 the developmental strategy for ABT-594 that had
4 been made by Abbott?

5 MR. PHILLIPS: Objection.

6 BY THE WITNESS:

7 A. Not by me -- not to me.

8 BY MR. DAVIS:

9 Q. To your knowledge, who would establish
10 the developmental strategy for ABT-594 within
11 Abbott?

12 MR. PHILLIPS: Objection.

13 BY THE WITNESS:

14 A. All I can tell you is it's levels much
15 higher than mine. Who specifically makes that or
16 generally makes that, I don't know.

17 BY MR. DAVIS:

18 Q. Do you know what an NNR is?

19 A. No. I do not.

20 Q. Did you ever participate with any -- in
21 any discussions within Abbott regarding any
22 programs to develop any NNR analgesics?

23 A. I -- no, that does not even ring a bell.

24 MR. DAVIS: Mark this as the next exhibit,

1 Do you see that?

2 A. Yes.

3 Q. Did you regard the tolerability issues
4 around ABT-594 in early March of 2001 to be a
5 potential issues, threats or negatives?

6 A. I don't -- I'm not the person that
7 determines what's tolerable and tolerability
8 issues. So, I mean, that's not what I do.

9 Q. Did you have any position on that issue
10 at that point in time?

11 A. No.

12 Q. As of early March 2001 did you think it
13 was likely that ABT-594 was going to continue to be
14 developed by Abbott to Phase III?

15 A. I thought it was, yes.

16 Q. Did you understand the results of the
17 114 trial to be such that Abbott had determined the
18 appropriate dose for ABT-594?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. I'm not sure what Abbott or that group
22 would have determined as the appropriate dose.
23 I -- I don't know. I don't know.

24 BY MR. DAVIS:

1 Q. -- that would weigh 559 pounds, is that

2 it?

3 A. Exactly.

4 Q. What is it about the other entry that

5 you would regard as --

6 A. Respiratory rate of 76 is pretty high.

7 Q. Is this part of the process of cleaning

8 up the data?

9 A. Yes, it is.

10 Q. Did you encounter any unusual problems
11 in cleaning up the data for the 114 study?

12 A. No.

13 Q. Cleaned up nicely?

14 A. Just like any, yeah, just like any other
15 trial, you know. Nothing struck me as unusual.
16 It's a long process.

17 MR. DAVIS: Mark that, please, as the next
18 exhibit.

19 (WHEREUPON, a certain document was
20 marked Collicott Deposition Exhibit
21 No. 38, for identification, as of
22 09-27-2006.)

23 BY MR. DAVIS:

24 Q. Ms. Collicott, I will show you what's

1 been marked as Exhibit 38 and ask you first if you

2 have seen this document before.

3 A. I have not.

4 Q. Have you seen documents in this format

5 before within Abbott?

6 A. Yes, similar documents.

7 Q. What context have you seen -- what are

8 they? Let me ask you.

9 A. I would say these are updates regarding

10 ABT-594 that would be given to upper management.

11 Q. Do you typically receive copies of these

12 updates when -- at or around the time that they are

13 issued?

14 A. Not generally.

15 Q. How did it come about that on prior

16 occasions you've seen documents like this?

17 A. Because on occasion I would see them,

18 but I would not have expected me to be on a

19 distribution list for this.

20 Q. Did you contribute in any way to the

21 creation of these documents to your knowledge?

22 A. Not to my knowledge.

23 Q. It's your understanding that these are

24 for senior management within Abbott?

1 A. I would say yes.

2 Q. Who or what organization within Abbott

3 was responsible for preparing documents like

4 Exhibit 38?

5 A. I don't know. It could be a combination

6 of groups. Who actually prepared it, I don't know.

7 Q. Were you on occasion solicited for

8 information for these reports, if you know?

9 A. No.

10 MR. PHILLIPS: I'm sorry. I didn't hear your
11 answer.

12 THE WITNESS: No.

13 MR. PHILLIPS: Thank you.

14 BY MR. DAVIS:

15 Q. Would you look at the second page of
16 Exhibit 38, please.

17 You see under "April 2001, Monthly
18 Highlights - Key Project Progress."

19 Do you see that?

20 A. Yes.

21 Q. There is a reference in the first bullet
22 point to "Blind broken on April 20 for M99-114
23 painful diabetic neuropathy Phase IIb study."

24 Do you see that?

1 May we mark this, please, as the next
2 exhibit.

3 (WHEREUPON, a certain document was
4 marked Collicott Deposition Exhibit
5 No. 39, for identification, as of
6 09-27-2006.)

7 BY MR. DAVIS:

8 Q. Ms. Collicott, you have what's been
9 marked as Exhibit 39. I ask you to look at it for
10 a moment and tell me if you have seen this document
11 before.

12 A. I don't remember.

13 Q. Did you participate in the preparation
14 of any PowerPoint presentations concerning the
15 results of the 114 study?

16 A. I don't remember.

17 Q. Is that something that you typically
18 would do as part of your clinical trial-related
19 duties?

20 A. I could have.

21 Q. Do you recall that that's something that
22 you typically are involved in?

23 A. Again, it depends on the group. Some
24 groups do this more than others.

1 Q. And more often than not in your

2 experience have you done that?

3 A. Looking at the first few pages I could

4 see that I could have done that. If you start

5 looking at the design and the outcomes, I would not

6 have done that.

7 Q. As you sit here today do you believe

8 that you participated in any way in the creation of

9 this presentation?

10 A. I don't remember.

11 Q. Do you know to whom this presentation

12 was made?

13 A. I don't, no.

14 Q. If you look at the last page of this

15 presentation.

16 A. Got it.

17 Q. There is a slide that begins "ABT-594

18 150, 225 and 300," and what's mcg?

19 A. Micrograms.

20 Q. Micrograms. BID stands for?

21 A. Twice a day.

22 Q. "Were associated with a dose dependent

23 increase in adverse events, especially nausea,

24 vomiting and dizziness."

1 Do you see that?

2 A. Yes.

3 Q. And do you recall helping to assemble

4 any of this information?

5 A. I don't recall that, no.

6 Q. Were you aware of this information

7 before you saw this document today?

8 A. Yes, I would have been aware of it from

9 reviewing tables and listings after the blind was

10 broken.

11 Q. After the blind was broken and you

12 reviewed this information, did you still believe it

13 likely that ABT-594 was going to be moved into

14 Phase III by Abbott?

15 A. I did.

16 Q. Was there any particular reason why you

17 thought that ABT-594 was more likely than not to be

18 moved forward?

19 A. Because it was very efficacious.

20 MR. DAVIS: Let's mark this, please, as the

21 next exhibit.

22 (WHEREUPON, a certain document was

23 marked Collicott Deposition Exhibit

24 No. 40, for identification, as of

1 A. I don't even remember because I can't
2 think of even who the commercial folks were, their
3 names. I can't remember.

4 MR. DAVIS: Mark this, please, as the next
5 exhibit.

6 (WHEREUPON, a certain document was
7 marked Collicott Deposition Exhibit
8 No. 42, for identification, as of
9 09-27-2006.)

10 BY MR. DAVIS:

11 Q. Ms. Collicott, you have Exhibit 42.
12 Would you take a moment, look at the document and
13 tell me if you have seen it before.

14 A. I don't remember seeing it.

15 Q. Who is Judith Brownell?

16 A. She was with our data management group.

17 Q. What is the release of the database?

18 A. That would be all queries have been
19 resolved and the database is locked.

20 Q. Now, I think you testified early today
21 that typically the study would not be unblinded
22 until the database had been locked?

23 A. That is absolutely right.

24 Q. Was this study, was the database in this

1 study -- strike that.

2 When was the database on this study

3 locked?

4 A. I don't remember.

5 Q. Can you tell from reading this e-mail

6 when it was locked?

7 A. Let me look at it again.

8 It appears to be June 18. If it was

9 transferred to statistics for analysis.

10 Q. Do you know why it was that the results

11 of this study were unblinded before the data for

12 this study was locked?

13 A. It shouldn't have been. And it wasn't.

14 Q. Well, if we look at Exhibit 38. Do you

15 have that in front of you?

16 A. I can find it.

17 Q. It's the April 1, 2001 -- I'm sorry.

18 It's the April 2001 status report. If you look at

19 the second page of that document it states that

20 "Blind broken on April 20." Do you see that?

21 A. Okay.

22 Q. Is that -- when they refer to blind

23 broken, is there any other blind other than the

24 blind on the data from the study that could be

1 broken as of that date?

2 A. No, that would be it.

3 Q. Then looking back at Exhibit 42, again,

4 you've indicated that this -- the data was

5 transferred to statistics on the 18th of June,

6 2001. You would agree with me that's subsequent to

7 April 20 of 2001?

8 A. Yes.

9 Q. So, it appears that in this case the

10 blind was broken before the data actually had been

11 locked, is that right?

12 MR. PHILLIPS: Objection.

13 BY THE WITNESS:

14 A. That's the thing with this wording, and

15 I probably shouldn't have said that because

16 transfer to statistics for analysis, I made the

17 assumption that meant database lock although

18 normally we always say database lock. So, I am not

19 following this.

20 Q. The subject of the e-mail that's

21 Exhibit 42 says "Release of Database." Is that the

22 same as locking the database?

23 MR. PHILLIPS: Objection.

24 BY THE WITNESS:

1 A. I don't know. I don't know.

2 BY MR. DAVIS:

3 Q. The date -- this e-mail that's

4 Exhibit 42 from Ms. Brownell to -- it's to you,

5 among others, correct?

6 A. Yes.

7 Q. And it says, "The Data Management

8 process has been completed for study M99-114

9 (ABT-594) and the database, MC114A, was transferred

10 to statistics for analysis on 18 June '01 at" 5 --

11 15:07."

12 Do you see that?

13 A. Yes.

14 Q. Would you agree with me that what this

15 is saying is that the data from that study was

16 completed and the data was transferred to

17 statistics for analysis at approximately 3:07 p.m.

18 on June 18, 2001?

19 MR. PHILLIPS: Objection.

20 BY THE WITNESS:

21 A. I don't know. I can only read what it

22 says, and because not being a data management

23 person, they may have had their own analyses that

24 they had to do after the blind was broken and then

1 transfer it to statistics for their analyses. But
2 not being stats or data management, I'm not sure
3 what their process is.

4 Q. Is there more than one database for the
5 study?

6 MR. PHILLIPS: Objection.

7 BY THE WITNESS:

8 A. A database can be unlocked to add
9 additional data that has come in and then relocked.
10 I don't know whether that occurred with this one.

11 BY MR. DAVIS:

12 Q. Do you have any recollection of that
13 occurring with respect to trial 114?

14 A. I don't remember. I mean it certainly
15 happens. If significant information comes in, it
16 happens it has to be unlocked and relocked. But
17 it's a -- it's a process. I don't recall whether
18 we unlocked the database of 114.

19 Q. How would one -- how would you go about
20 determining today when it was that the database for
21 the 114 trial was locked?

22 A. I would contact data management.

23 Q. Is that located in Abbott Park?

24 A. Yes.

1 perspective would be data management?

2 A. That's where I would go.

3 Q. As you sit here today you don't recall

4 Abbott ever unlocking and then relocking the data

5 for trial 114?

6 A. Right, I don't recall.

7 MR. DAVIS: Let's mark this, please, as the

8 next exhibit. 43, I believe.

9 (WHEREUPON, a certain document was

10 marked Collicott Deposition Exhibit

11 No. 43, for identification, as of

12 09-27-2006.)

13 BY MR. DAVIS:

14 Q. Ms. Collicott, I show you what's been

15 marked as Exhibit 43, ask you to look at it for a

16 moment and tell me if you have seen it before.

17 A. No, I have not.

18 Q. It appears to be one of those monthly

19 status reports concerning ABT-594, this one dated

20 from July of '01.

21 If you look at the second page of the

22 document, under "Monthly Highlights." Do you see

23 that?

24 A. Yes, I do.

1 needed to find other jobs. So that's how I knew.

2 Q. Did Mr. -- Dr. McCarthy explain to you
3 in any shape, manner or form the reasoning behind
4 Abbott's decision to terminate development of 594?

5 A. No. At least not that I can remember.

6 MR. DAVIS: Will you mark this as the next
7 exhibit, please.

8 (WHEREUPON, a certain document was
9 marked Collicott Deposition Exhibit
10 No. 45, for identification, as of
11 09-27-2006.)

12 BY MR. DAVIS:

13 Q. Were you curious as to why Abbott had
14 decided to terminate development of 594?

15 A. I was disappointed. Curious, no,
16 because that's the nature of the business. I've
17 been on many compounds that never see the light of
18 day.

19 Q. To your knowledge, did Abbott's decision
20 to terminate further development of 594 have
21 anything to do with the results of the 114 study?

22 A. I don't know.

23 Q. Did it have anything to do with the
24 tolerability of 594?

1 Q. Looking again at Exhibit 45, is that in

2 fact an e-mail that you sent to Jan Lips?

3 A. Yes.

4 Q. Is that the correct name, Jan Lips?

5 A. Yes.

6 Q. In the e-mail, which is dated October 5,

7 2001, you state, second paragraph, "ABT-594 is on

8 life support but they haven't pulled the plug yet."

9 A. Um-hmm.

10 Q. What did you mean by that?

11 A. Basically that the project was still

12 ongoing.

13 Q. You regard a project that's on life

14 support as --

15 A. Yes.

16 Q. -- as ongoing?

17 A. Yes, until it's killed, yes.

18 Q. Did you regard it as being something

19 less than healthy as of October 2001?

20 A. I -- it's hard to explain. Less than

21 healthy, no. As with any trials that we do, you

22 never know when funding is going to be pulled. You

23 never know what the reasoning is behind it. It's

24 just one of those things that happens.

1 So, the plug hadn't been pulled on it
2 yet. It hadn't been killed. We were planning,
3 doing some additional planning for additional
4 studies. And that's -- that's what that was.

5 Q. When was the last time you saw this
6 e-mail?

7 A. This one I saw yesterday.

8 Q. By referencing "ABT-594 is on life
9 support," did you mean to convey by that that you
10 thought it was more likely than not that ABT-594
11 would be moved on to Phase III?

12 A. I still believed it would be moved on to
13 Phase III.

14 Q. You thought it more likely than not?

15 A. Yes.

16 Q. And that equates to being on life
17 support?

18 A. It's just an Abbott term. It's what we
19 say. It's what we do. This is just a personal
20 e-mail, you know, back-and-forth sort of thing. I
21 believed we were moving forward with that trial as
22 yet. I had hoped we were. And you could have
23 knocked me over with a feather when I found out we
24 weren't.

1 Q. So, you were surprised when you learned
2 that ABT-594 was not going to be further developed
3 by Abbott?

4 A. Yep.

5 MR. DAVIS: Let's mark this, please, as the
6 next exhibit.

7 (WHEREUPON, a certain document was
8 marked Collicott Deposition Exhibit
9 No. 46, for identification, as of
10 09-27-2006.)

11 BY MR. DAVIS:

12 Q. Ms. Collicott, you have in front of you
13 a monthly status report for ABT-594 dating from
14 October of 2001. At least that's what it purports
15 to be on its face.

16 Have you seen this document before?

17 A. I have not.

18 Q. If you take a look at the second page of
19 the document under "Monthly Highlights" it
20 says, "Program is not funded for 2002 -
21 Outlicensing activities initiated."

22 Do you see that?

23 A. Yes.

24 MR. PHILLIPS: I'm sorry. Where are you?

1 BY MR. DAVIS:

2 Q. And is it your recollection that even as
3 of September '01 you thought that ABT-594 was more
4 likely than not going to continue to be developed
5 by ABT?

6 A. I was hoping it would continue to be
7 developed. I know how these things go with first
8 you're funded, then you're not, then you are, then
9 you're not. So it's nothing new and I expected us
10 to continue, yes.

11 Q. It says, "For the 2002 planning process,
12 we are still assumed to be an unfunded, but there
13 is a chance that we will be back in the race for
14 funding once the preliminary cost and time for a
15 Phase IIb, Part 2 study are reviewed with Jeff."

16 Did you participate in the process of --
17 in any way of determining funding for ABT-594 for
18 future years?

19 A. I don't recall. If I did, it would be
20 simply determining the cost of a CRO. Not any sort
21 of big budget planning. It would just be the
22 day-to-day running of my portion of a clinical
23 trial, which is just a tiny part of it.

24 Q. If you take a look at the second page of

ERRATA SHEET FOR THE TRANSCRIPT OF:

Case Name: Hancock v. Abbott Labs
 Dep. Date: September 27, 2006
 Deponent: Marilyn J. Collicott

CORRECTIONS:

Pg.	Ln.	Now Reads	Should Read	Reasons Therefore
5	12	Mr.	Ms.	incorrect
9	7-8	human... Government	... trial conducted in humans that may or may not be conducted using drugs not yet approved by the FDA.	clarification
19	10	is	are	grammar
28	2nd 3	is, is	are, are	grammar
52	1	is	are	grammar
57	12	PS	Case	correction
64	9-10 ¹⁸	TARD	PARD	correction
113 ¹⁵	18-19	HEUSER	HEUSER	correction
166	14	woiDAT	woiDAT	correction
276	22	in the	and the	correction
287	17	Freehof	Freehoff	correction

M. J. Collicott 31 OCT 06
 Signature of Deponent

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE)
COMPANY, JOHN HANCOCK VARIABLE)
LIFE INSURANCE COMPANY and)
MANULIFE INSURANCE COMPANY)
(f/k/a/ INVESTORS PARTNER)
INSURANCE COMPANY),)

Plaintiffs,) Civil Action No.

-vs-) 05-11150-DPW

ABBOTT LABORATORIES,)
Defendant.)

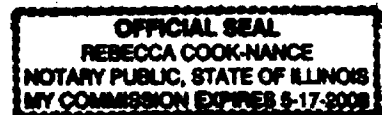
I hereby certify that I have read the
foregoing transcript of my deposition given at the
time and place aforesaid, consisting of Pages 1 to
295, inclusive, and I do again subscribe and make
oath that the same is a true, correct and complete
transcript of my deposition so given as aforesaid,
and includes changes, if any, so made by me.


MARILYN J. COLLICOTT

SUBSCRIBED AND SWORN TO
before me this 1ST day
of NOVEMBER, A.D. 2006.

Notary Public





Collicott Deposition Exhibit 1

D's Exhibit I



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
05/09/2000 01:08 PM

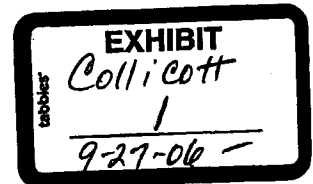
To jc@wilmingtongroup.com@internet
cc
bcc
Subject resume

JC

Here's my resume - call if questions. Thanks.....mc



resume'00.doc



Highly Confidential

ABBT242357

MARILYN J. COLLICOTT
Clinical Project Manager
6220 South 121 Street
Hales Corners, WI 53130
(414) 529-3282
(847) 938-1199

SUMMARY OF EXPERIENCE - More than thirteen years experience in clinical research and quality assurance/quality control. Experienced in GCP, GMP, GLP, clinical project management, clinical monitoring, quality auditing, process validation, and laboratory management in the pharmaceutical and medical device industries.

Education BA in Chemistry and Biology
Alverno College, Milwaukee, WI

Employment History

Abbott Laboratories - Abbott Park, IL
Pharmaceutical Products Division - Analgesia Venture

1999 - Present **Clinical Project Manager**

- * Complete project management of ABT-594 Phase IIb osteoarthritis clinical trial. To include: CRO selection and management, investigator identification and selection, protocol writing, CRF design, planning and conduct of investigator meetings, day-to-day study direction, initiation and management of all related budgets and contracts, workforce planning, training, etc.
- * Assist Venture Head and Associate Medical Director with Operations aspects of the Venture to include long-term budget planning, facilitation of product development and clinical trial team meetings, prepare Monthly Updates, Venture contact/liaison for PPD product development team members.
- * Complete yearly IND Update and Investigator's Brochure.
- * Member SOP Steering Committee.

1998 - 1999 **Senior Clinical Research Associate**

- * Project management of ABT-594 Phase II clinical trials (osteoarthritis and post-op pain).
- * Assist with project management of ABT-594 Phase II neuropathy trial
- * Manage the Analgesia Venture Review Team consisting of 5 medical reviewers and 1 document clerk/tracker.

Pharmaceutical Products Division - Immunoscience Venture

1996 - 1998 Senior Clinical Research Associate

- * Complete project management of Abbott cyclosporine de novo kidney transplant study including site selection, advisory and investigator meeting planning, workforce allocation, and long-term project management.
- * Complete project management of Phase I clinical trials for ABT-491 to including CRO selection and management, study start-up and long-term management.
- * Project management mentor for junior CRAs.
- * Presenter at investigator meetings and in-house functions.
- * Managed investigator IND for zileuton.

1993 - 1996 Clinical Research Associate

- * Clinical monitoring of Phase III investigational drug trials.
- * Preparation of clinical trial sites for QA and FDA audits.
- * Authoring and management of Phase III clinical protocols.
- * Provide training for new or inexperienced CRAs.
- * Preparation of written study summaries.
- * Participated in numerous aspects of NDA filing for zileuton (Zyflo) and ritonavir (Norvir).

**Surgitek, Inc. - Racine, WI
(Former Division of Bristol-Myers Squibb)
1986-1992**

Acting Manager, Quality Assurance/Quality Control

- * Directly managed a staff of 16 including 2 supervisors.
- * Proposed, directed, and implemented QA projects related to the product lines and to the sale of the company.
- * Developed and implemented plan for cross-training in all areas of QA/QC resulting in a highly skilled workforce able to step in as needed in areas requiring additional coverage.
- * Served as QA/QC advisor on all new product/project teams.
- * Appointed to Internal Business Planning Committee targeting future endeavors designed to move the company forward during the sale and transition.

Quality Assurance Compliance Supervisor

- * Scheduled and performed all internal GMP audits.
- * Developed methods for and performed vendor component, final product, laboratory, and sterilization facility audits in the U.S. and Europe.
- * Revised and implemented new QC inspection procedures.

Quality Assurance Supervisor

- * Completed the validation of 2 new contract sterilizers.
- * Completed in-house sterilization validation for newly developed product.
- * Researched, developed, and recommended a cost savings plan to institute parametric release of steam sterilized products with an estimated cost savings of \$106,000. annually.
- * Set up internal systems and utilized standards to assure biocompatibility requirements for components and devices.

Biolaboratory Supervisor: Responsible for the day-to-day operations of the labs providing biological and chemical tests to support production, R&D, and QC.

New Materials Evaluation Technician: Responsible for initiating protocols and final reports for recommended testing on all new materials, products and processes.

Revised 2/9/00

Collicott Deposition Exhibit 2

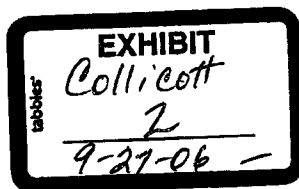
P's Exhibit BV

Part 1

ABT-594 DEVELOPMENT PLAN



June, 1999



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ABBT 0018986



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ABBT 0018987



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ABBT 0018988

ABT-594

EXECUTIVE SUMMARY

June, 1999

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ABBT 0018989

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

1

A. EXECUTIVE SUMMARY

A.1 Introduction

A.1.1 The Disease Class

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at \$100 billion a year in direct and indirect costs. Approximately 95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain. Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

A.1.2 Drug Class and Pharmacological Characteristics

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 is anticipated to be effective for the treatment of both acute and neuropathic pain. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

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Development Plan
ABT-594

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ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. *In vitro* and *in vivo* studies show that the antinociceptive actions of ABT-594 are blocked by nicotinic acetylcholine receptor (nAChR) antagonists, but not by opioid receptor antagonists supporting a mechanism of action that involves nAChR modulation.

ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes. ABT-594 also selectively prevents the activation of dorsal horn neuron responses to noxious mechanical and thermal stimuli, without having effects on non-noxious mechanical and thermal stimuli that could impair sensory perception.

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Development Plan
ABT-594

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A.2 Commercial

A.2.1 ABT-594 Target Profile

PPCC/ODC Profile (9/99, 1Q01)	Current Profile (9/99, 1Q01)	Rationale for Profile Change	Probability	Status	Share Impact
Indicated for the treatment of pain (general pain claim)	Indicated for the treatment of osteoarthritis pain	"General pain" claim not achievable due to slow onset of action; proof of principle established in molar extraction study	Medium	9/99, 1Q01	High
Effective in neuropathic pain	Indicated for the treatment of neuropathic pain	Indication specific claims now favored since general pain claim not achievable	Low	9/99, 2Q01	Medium
Effective for moderate to moderately-severe pain	N/A	No longer applicable without general pain claim	N/A	N/A	N/A
Not scheduled	No change	N/A	High	4Q02	High
Improved safety profile compared to opioids including: - less GI motility impairment - less respiratory depression - low tolerance potential - no dependence/withdrawal	No clinically significant tolerance, dependence or withdrawal	Simplify profile to focus on the most commercially important AEs	Medium	2Q01	High
	Very few abnormal LFTs	Abnormal LFTs in a few Phase I subjects	High	9/99	High
	Very low nausea/vomiting at effective dose	Relatively high incidence of nausea/vomiting in single dose Phase I & II subjects (food and dose dependent)	Medium	9/99	High
	Other safety OK	Simplify profile	Medium	9/99, 2Q01	High
	No significant or sustained differential efficacy in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	Low	9/99, 2Q01	High
	No significant or sustained differential side effect profile in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	High	9/99, 2Q01	Medium
	No re-initiation of cravings in ex-nicotine users	Possible due to nicotinic mechanism	Medium	2Q01	High

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Development Plan
ABT-594

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A.2.1 ABT-594 Target Profile (Continued)

PPCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Onset of action in less than 30 minutes	Onset of action comparable to other therapies used to treat OA	Onset of action estimated at 90 minutes in Phase II trial	Low	9/99	Medium
	Onset of action comparable to other therapies used to treat neuropathic pain	Onset of action estimated at 90 minutes in Phase II trial	High	9/99	Medium
BID/TID dosing	BID dosing	Competitive dynamics highlight importance of dosing convenience	High	9/99	Medium
No major drug interactions, especially with drugs used for common chronic conditions	No change	N/A	High	4Q00	Medium

A.2.2 Forecast

U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rx's (MM)	280	285	291	297	303
- % chg	2%	2%	2%	2%	2%
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rx's (MM)	2.8	7.1	11.1	13.3	15.1
Price/Rx (\$)	34.97	35.67	36.39	37.12	37.86
Abbott Sales (\$MM)	125	254	402	495	573
R&D (\$MM)	5	5	4	4	3
SG&A (\$MM)	66	98	90	85	84
SMM (%)	97.2	97.3	97.3	97.4	97.4
Div. Margin (\$MM)	59	162	324	427	509

10 year pre-tax NPV @ 12.5% = \$1.016 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$587 MM

10 year post-tax ENVY @ 12.5% = TBD

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

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Key assumptions:

- Assumes 12/97 PPCC profile
- NDA Filed 12/01, Launch 6/03
- First in class ChCM
- Usage = 70% chronic and 30% acute
- Weighted average days per Rx = 15.6
- Stocking at 12% of first year's sales
- Detailing includes 30% of IMs, 25% of FPs and GPs, 25% of Rheumatologists, and 10% of Neurologists
- Sampling at 80% of details at launch, 8 units per detail, 5 days of therapy per unit
- Patent expires 12/2016

Forecast Update Plan:

Forecast will be updated in late June/early July 1999 to account for revised indications of OA and/or neuropathic pain and the associated spillover use in other pain states. Forecast will be available well in advance of ABT-594 Go/No Go decision in 9/99.

Ex-U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rx's (MM)	-	-	-	-	-
- % chg					
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rx's (MM)	-	-	-	-	-
Price/Rx (\$)	-	-	-	-	-
Abbott Sales (\$MM)	60	150	250	300	320
R&D (\$MM)	3.4	3.2	2.8	2.4	2.0
SG&A (\$MM)	27	53	50	48	45
SMM (%)	95%	95%	95%	95%	95%
Div. Margin (\$MM)	26	85	182	235	251

10 year pre-tax NPV @ 12.5% = \$428

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$253

10 year post-tax ENVY @ 12.5% = TBD

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

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Key assumptions:

- First in class ChCM
- Indicated for treatment of moderate to moderately-severe pain
- Effective in neuropathic pain
- Good tolerability and safety profile
- No nicotinic effects
- Launched in all AI regions, including Japan, simultaneously (2003)

Forecast Update Plan:

- Forecast will be updated 9/99 (in time for the Go/No Go decision) to reflect results of marketing research to be conducted 3Q 1999 regarding expected uptake of 594 in OA and neuropathic pain markets, as well as potential spill-over prescribing for other pain states.

Global Forecast

	2003	2004	2005	2006	2007
U.S. Sales (\$MM)	125	254	402	495	573
Ex-U.S. Sales (\$MM)	60	150	250	300	320
Total Sales (\$MM)	185	404	652	795	893
Total Division Margin (\$MM)	85	247	506	662	760

10 year pre-tax NPV @ 12.5% = \$1.44 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$840 MM

10 year post-tax ENVY @ 12.5% = TBD

A.3 Clinical Development

A.3.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Given the spectrum of analgesic activity of ABT-594 in preclinical animal models of pain, the clinical development program for ABT-594 will evaluate the safety and efficacy of ABT-594 for the treatment of neuropathic pain and pain associated with osteoarthritis. In addition, pilot studies are planned to assess the safety and efficacy of ABT-594 for the treatment of pain associated with cancer.

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Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Indication (Study Type)	Phase II		Phase III		Phase IIIb	
	# Studies	# Patients	# Studies	# Patients	# Studies	# Patients
Osteoarthritis						
U.S.	1 ^c	250	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Neuropathic Pain						
U.S. ^a	1 ^c	150	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Cancer Pain						
U.S.	2	500	-	-	-	-
Long-Term Safety						
U.S.	-	-	1 ^a	600 ^d	-	-
Europe	-	-	1 ^a	300 ^d	-	-
Pricing Studies						
U.S.	-	-	-	-	1	500
Europe	-	-	-	-	1	500
Canada	-	-	-	-	1	500
Australia	-	-	-	-	1	500
TOTAL	4	900	12	5400	4	2000

^a Registration Trial

^b Bridging Study

^c Ongoing

^d Patients already counted in Phase III osteoarthritis and neuropathic pain studies.

A.3.2 Cost Through NDA

Year	Cost
1999	29.9
2000	93.2
2001	50.5
Total Cost	173.6

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A.3.3 Development Milestones

The project milestones for ABT-594 are as follows:

Milestones	Date
PPCC Approval	12/96
Start Funding	1/97
Go/No Go Preclinical Safety	6/97
Start Phase I Europe	7/97
File IND (Liquid)	2/98
Start Phase II U.S.	7/98
Go/No Go Clinical Efficacy	9/99
File CTX/CTN	10/99
End of Phase II Mtg. w/FDA	11/99
Start Phase III U.S./Europe	12/99
Start Phase I Japan	2/00
Start Phase III Bridging Japan	1/01
File Europe - EMEA	12/01
File U.S. NDA - FDA	12/01
File Japan - Koseisho	6/02
Regulatory Approval U.S.	6/03

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A. BACKGROUND AND RATIONALE

A.1 Drug Class and Pharmacological Characteristics

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 is anticipated to be effective for the treatment of both acute and neuropathic pain. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. *In vitro* and *in vivo* studies show that the antinociceptive actions of ABT-594 are blocked by nicotinic acetylcholine receptor (nAChR) antagonists, but not by opioid receptor antagonists supporting a mechanism of action that involves nAChR modulation.

ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes. ABT-594 also selectively prevents the activation of dorsal horn neuron responses to noxious mechanical and thermal stimuli, without having effects on non-noxious mechanical and thermal stimuli that could impair sensory perception.

A.2 The Disease Class

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at \$100 billion a year in direct and indirect costs. Approximately

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95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain. Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

A.3 Pathophysiology and Treatment Options

The normal response to a brief noxious stimulus, producing negligible tissue injury, serves to warn and protect the individual from potential injury. This is the "ouch" type of pain evoked by briefly touching a hot surface, or by a pin prick. Pain is perceived when the high-intensity noxious stimulus (e.g., heat or a pin prick) activates C and A δ primary afferent nociceptive nerve fibers. The resulting impulse from the periphery reaches the dorsal horn of the spinal cord, where it is processed and transmitted to the brain. Efferent, descending pathways can also modulate the afferent impulse at the dorsal horn, probably via monoamine dependent mechanisms. Low intensity stimuli, like touch, which are transduced along A β fibers, are not perceived as painful in the absence of tissue injury.

In the setting of trauma, infection, surgery, burns or inflammatory diseases, a diverse range of inflammatory mediators (e.g., cytokines, kinins, prostaglandins) are synthesized and released at the site of tissue injury and inflammation, and they activate and sensitize local nociceptors (nociceptive pain). The sensitized nociceptors become spontaneously

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active, they respond in an exaggerated fashion to normally mildly painful stimuli (hyperalgesia), and they can then be activated by normally non-noxious stimuli such as light touch (allodynia). This phenomenon, known as peripheral sensitization, is thought to account for primary hyperalgesia, e.g., increased pain and tenderness at the site of injury.

The ongoing barrage of C-fiber impulses arriving from the sensitized periphery also triggers hyperexcitability of neurons in the spinal cord (central sensitization) and contributes further to allodynia and hyperalgesia.

Osteoarthritis pain results from activation of pain fibers in the periosteum, at the insertion point of tendons and synovia, from pressure within the joint and, to a minor extent, inflammatory pain in and around the joint. Although not well recognized, osteoarthritis pain (like any chronic painful condition) is probably associated with peripheral and central sensitization.

Neuropathic pain results from injury to the central or peripheral nervous system due to a variety of causes including trauma, surgery, disease, and certain drugs. Following nerve injury, a number of changes occur in the periphery which contribute to abnormal painful sensations. The damaged nerve may begin to discharge spontaneously at atypical (ectopic) locations, including the neuroma and demyelinated zones at the site of nerve injury, and the associated dorsal root ganglion (DRG). These ectopic discharges produce spontaneous burning pain. In addition, the increased barrage of impulses from the periphery leads to hyperexcitability of spinal cord dorsal horn neurons (central sensitization), resulting in hyperalgesia and allodynia.

Inflammatory and neuropathic pain can co-exist. For example, a cancer patient may experience inflammatory pain following surgery or due to inflammation and tissue damage at the site of the tumor, and neuropathic pain due to radiation or chemotherapy induced neuropathies, or due to tumor encroachment on the peripheral nervous system.

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Table 1. Prevalence of Pain by Diagnosis¹

Diagnosis	Prevalence (MM)	
	U.S.	Worldwide ²
Musculoskeletal Pain	56	160
Post-Operative Pain	30	83
Neuropathy (Diabetic, PHN, etc.) Pain	28	75
Osteo/Rheumatoid Arthritis Pain	17	46
Cancer Pain	2	5
Total Pain Diagnoses	133	359

1. Decision Resources, 1996. Data reflect number of pain diagnoses such that a patient might be diagnosed with two pain diagnoses of different pain types at separate visits.

2. Germany, France, Italy, Spain and Japan.

Prescription analgesics for pain other than headache can be broken down into three major categories: **opioids, non-opioids, and adjuvant analgesics.**

Opioids analgesics such as morphine and codeine, are generally used for the treatment of moderate to severe pain and are often added when pain is inadequately controlled by acetaminophen and/or NSAIDs. Opioid analgesics are used primarily for the pain associated with surgery, injuries, musculoskeletal disorders, and cancer pain. Opioids are considered the drug-of-choice for severe acute pain and cancer pain. Although highly efficacious, opioids are associated with a significant number of side effect liabilities. Constipation is the most common adverse event associated with opioid therapy, and prophylactic laxatives are widely prescribed with opioids. Nausea and vomiting, sedation and cognitive impairment are also often encountered. Respiratory depression, while less frequent, is the most dangerous side effect of opioid therapy. In addition to the fear of respiratory depression, concerns about addiction, tolerance, use diversion and the fear of regulatory action ("opiophobia") have all proven to be significant impediments to the use of opioids. Opioids are generally not prescribed for chronic non-malignant pain conditions due to patient tolerance and the potential for addiction. Opioids are scheduled compounds that are subject to Drug Enforcement Agency (DEA) regulations, impacting

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prescribing and product distribution. The extent of the regulations are based on the abuse potential of each product; the higher the abuse potential, the more restrictive the control over distribution.

Opioid analgesics can be divided into opioid and opioid-combination agents. Opioids are either derivatives of opium or synthetic agents with opium-like properties. Opioids produce analgesia by binding to various opioid receptors, which in turn decrease pain perception within the central nervous system but do not affect the source of pain or reduce inflammation. Opioid-combination agents combine an opioid agent with another analgesic such as aspirin or acetaminophen. The advantage of this type of combination agent lies in its broad pain coverage. The aspirin or acetaminophen acts on the peripheral nervous system while the opioid decreases the degree of pain experienced by the central nervous system.

Non-opioid analgesics are used for the management of mild to moderate pain and as an adjunct to the opioids in the management of moderate to severe pain. They are generally used in chronic pain syndromes and when pain severity is mild to moderate. Non-opioid agents can be divided into non-steroidal anti-inflammatory drugs (NSAIDs) and other non-opioids. Prescription NSAIDs are used to treat osteoarthritis, rheumatoid arthritis, lower back pain, and other chronic pain conditions in addition to some mild to moderate acute pain conditions. NSAIDs inhibit the synthesis of prostaglandins, substances released by the body after trauma and which are responsible for inflammation, increased body temperature and the sensitization of pain receptors. NSAIDs generally have fewer CNS side effects than do opioid agents. However, NSAIDs may cause potentially serious GI side effects including gastric ulceration and bleeding. COX-2 agents may cause fewer GI side effects, but do not improve upon the analgesic efficacy of NSAIDs.

Currently, NSAIDs are the primary treatment for pain associated with osteoarthritis. Recently approved COX-2 inhibitor agents are likely to make significant incursions into the NSAID market especially in the elderly patient population on chronic therapy at risk for GI bleed. The NSAIDs and acetaminophen are associated with a "ceiling effect" for their analgesia, i.e. complete pain relief cannot be achieved, even after dose escalation, which significantly limits their utility to treat severe pain. Acetaminophen has analgesic

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and antipyretic activity, but lacks anti-inflammatory activity. The mechanism of action of acetaminophen is poorly defined, but appears to involve effects in the CNS. Acetaminophen has no effects on platelet function and no gastrointestinal toxicity, but may be hepatotoxic particularly in heavy drinkers and patients with chronic liver disease.

Other non-opioid analgesics include Ultram (tramadol HCl), which was approved in the U.S. in 1995 after more than 15 years of use in Europe. Tramadol is an analgesic that has an indication for the treatment of moderate to moderately-severe pain. The product has a unique dual mechanism of action via opioid and non-opioid mechanisms, and is not currently scheduled. Tramadol may, however, reinitiate physical dependence in previously opioid-dependent patients. It is recommended that tramadol not be used in opioid-dependent patients, in patients with a tendency to abuse drugs, or in patients chronically using other opioids. In addition, tramadol is under postmarketing surveillance for abuse potential, and may eventually receive scheduling status.

Adjuvant analgesics are drugs that are used for pain relief, but also have other significant indications (antiepileptic, antidepressant). The analgesic adjuvants include a number of compounds which have primary indications other than pain control, but have been found by clinical experimentation to have analgesic activity in certain types of pain. The onset of pain relief with adjuvant agents is frequently delayed due to the need for dose titration to minimize toxicities and for adaptive mechanisms to be induced. In addition, adjuvant agents are associated with significant toxicities. These drugs are most commonly used to treat the many types of neuropathic pain but have modest efficacy. A significant number of neuropathic pain patients, however, are treated with NSAIDs, muscle relaxants and non-opioid analgesics, despite their ineffectiveness. Opioids may be effective in neuropathic pain but are generally avoided because of abuse liability. The most common drug classes used as adjuvants are tricyclic antidepressants and antiepileptic drugs, which tend to have fairly significant side effect profiles. The only drug with a specific indication for any type of neuropathic disorder is Tegretol (carbamazepine) for trigeminal neuralgia. Generally, the use of adjuvant analgesics to treat neuropathic pain is based on trial and error using sequential drug trials.

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Gabapentin has a significant portion of its sales as off-label use in the treatment of neuropathic pain. Gabapentin, an anti-epileptic agent, has been used in neuropathic pain largely based upon trial and error. More recently, two placebo-controlled, double blind randomized trials demonstrated gabapentin's efficacy in pain associated with diabetic peripheral neuropathy (a type of distal symmetric neuropathy) and in post-herpetic neuralgia. While gabapentin's effect is modest, its success is largely attributable to the large unmet need in neuropathic pain and to the paucity of adverse events associated with gabapentin.

Recent findings in the understanding of pain mechanisms have led to a new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the $\alpha 2\delta$ calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability. A significant unmet need exists in the pain management market for products that are safer, non-abusable, non-addicting, non-scheduled, non-tolerance producing, and efficacious in oral and parenteral forms for the treatment of moderate to severe pain, especially for chronic nociceptive and neuropathic pain.

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B. COMMERCIAL

B.1 Market Overview

Pain is the most common symptom for which individuals seek medical assistance. Pain is the primary complaint of 50% of all patients who visit a physician. In 1996, the worldwide diagnosed pain population was 427 million, of whom 37% were from the U.S. and 63% from outside the U.S. Physician or patient concern about drug safety and side effect profiles, fear of addiction, the use of OTC therapies, or non-pharmacological treatments account for the 30-50% of patients who seek treatment for pain but are not prescribed an analgesic. Chronic pain sufferers may account for as much as 10-20% of the adult population, one-fourth to one-half of which obtains inadequate pain relief.

Pain is categorized by duration (acute or chronic) and by severity into one of three segments: mild, moderate, and severe. The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen, ibuprofen and other NSAIDs. The moderate and severe segments of the market have many opioid product offerings that are mostly generic, undifferentiated and inexpensive. Many patients, however, develop tolerance to these drugs, and opioids are scheduled products that create administrative burdens and barriers to prescribing. These barriers are particularly high in European markets. As a result, opioid use is restricted almost entirely to cancer pain, and there exists a large unmet need for effective treatment of severe pain. Prescription NSAIDs are generally written for chronic pain of moderate severity, though potentially serious GI or renal side effects may complicate treatment.

Total U.S. sales of prescription pain medications reached over \$5.1 billion in 1998. While opioids and combination opioids accounted for the majority of analgesic prescriptions at 55%, NSAIDs had the highest share of total prescription analgesic sales at 37%.

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The prescription pain market is made up of three classes of analgesics; opioids (and combination products), NSAIDs and other non-opioids (including aspirin and acetaminophen). Anesthetics, anti-migraine and adjuvant analgesics are not included in this market definition. The following tables show U.S. and ex-U.S. prescription and sales volume by class for 1998.

Table 2. 1998 Prescription Pain Market, Rx by Analgesic Class

Class	1998 U.S. TRx (M)	U.S. TRx CAGR '95-'98	1998 ex-U.S. TRx (M)	ex-U.S. TRx CAGR '95-'98
Opioids	143,843	6.2%	N/A	N/A
NSAIDs	79,928	(2.5%)	N/A	N/A
Other Non-Opioids	37,463	7.5%	N/A	N/A
TOTAL	261,234	3.5%	N/A	N/A

Source: IMS

Table 3. 1998 Prescription Pain Market, Sales by Analgesic Class

Class	1998 U.S. Sales (\$MM)	U.S. Sales CAGR '95-'98	1998 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '95-'98
Opioids	\$1,905	16.3%	\$682	14.8%
NSAIDs	\$1,926	(1.1%)	\$3,978	(2.5%)
Other Non-Opioids	\$1,328	(5.4%)	\$1,391	1.7%
TOTAL	\$5,159	3.0%	\$6,050	(0.1%)

Source: IMS; Ex-U.S. data includes retail pharmacy data from all audited markets and hospital data from major European markets and Canada only.

In the U.S., opioid analgesics are considered the drugs-of-choice for acute pain, especially of moderately-severe to severe intensity. Opioids are generally not prescribed for chronic pain conditions due to patient tolerance and the potential for addiction,

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although opioids are the most commonly prescribed medication for moderate to severe cancer pain. Ex-U.S. opioid use varies considerably from one country to another. The UK, France and Japan are more advanced than other ex-U.S. countries regarding their perspective on safe opioid use, and prescriptions have increased considerably over the past 5 years. In Italy, Spain and Germany, opioid use is extremely restricted, requiring patient identity cards and special prescription forms that must be obtained, in person, by the physician. Strong opioids such as morphine are often considered last resort. In both the U.S. and ex-U.S., opioids are government-scheduled products with restricted prescribing and product distribution.

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used in chronic pain syndromes and when pain severity is of mild to moderate intensity. NSAIDs exhibit analgesic and mild anti-inflammatory properties, and thus are drugs-of-choice in such pain conditions as osteoarthritis, rheumatoid arthritis and lower back pain. NSAIDs have fewer side effects than do opioid agents, especially CNS effects. However, the products can cause potentially serious renal and gastrointestinal side effects including gastric ulceration and bleeding.

"Other non-opioids" are defined as (1) non-opioid/non-NSAID agents like aspirin, acetaminophen or tramadol, or (2) NSAIDs that are positioned and marketed as analgesics, such as ketorolac or bromfenac sodium. Other non-opioids are generally used in place of opioids to treat moderate pain, or in some cases, moderately-severe pain.

Osteoarthritis (OA) is one of the largest segments of the analgesia market, and one of the most common conditions treated by primary care physicians. Over 35 million people worldwide suffer from OA, and three-fourths of OA sufferers surveyed indicate that the disease interferes with daily activities. Estimates of worldwide sales of prescription analgesics to treat OA range from \$2.25-3 billion. According to a recent study, as many as 47% of Americans diagnosed with OA take a prescription analgesic at least occasionally for the condition. NSAIDs and acetaminophen are the standard treatments for OA. However, the new COX-2 inhibitors are expected to grow the OA market due to their expected higher levels of GI safety. This added safety would attract patients who were administered prescription or OTC NSAIDs only occasionally to avoid potentially

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severe gastric ulcerations and bleeding. The COX-2 inhibitors will also take share from branded and multisource prescription NSAIDs. As a result, the COX-2 inhibitors are expected to grow the OA market in prescriptions and sales, maybe by a significant amount.

Neuropathic pain is a very large, yet largely untapped market. Estimates vary widely for the number of worldwide sufferers, from as low as 20 million to as high as 50 million or more. The number of actual cases is difficult to estimate since neuropathic pain is difficult to diagnose, and is often misdiagnosed. Neuropathic pain is often treated with adjuvant analgesics such as tricyclic antidepressants, anticonvulsants and alpha adrenergic agonists. Prescription drug sales for the treatment of neuropathic pain exceed \$1 billion worldwide. In the U.S. alone, approximately \$250 million of the sales of the anticonvulsant Neurontin (gabapentin) are off label uses attributed to the treatment of neuropathic pain. However, a significant unmet need exists in the treatment of neuropathic pain since few medications provide complete pain relief and most adjuvant medications have significant side effects that preclude their long-term use. As more effective and tolerable medications become available, the neuropathic pain market is expected to experience significant growth.

Most analgesics are indicated for the treatment of one or more specific pain states. However, depending on its characteristics, a significant amount of a product's prescriptions may come from non-indicated pain states (i.e., spillover prescriptions). Therefore, a product indicated for OA is likely to be prescribed for chronic lower back pain, rheumatoid arthritis, and other pain states with similar clinical characteristics or etiologies.

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B.2 Pipeline

Table 4. Analgesia Pipeline – Key Novel Agents

Product	Company	Mechanism	Phase	Comment
pregabalin	Parke-Davis	Ca channel blocker	III	Neuropathic pain, chronic pain Follow-up to Neurontin
JTE 522	Japan Tobacco/J&J	COX-2 inhibitor	II	J&J has rights outside Japan
4030W92	Glaxo	Na channel blocker	II	Acute and chronic pain
vedaclidine	Lilly	muscarinic agonist	II	General pain MOA losing favor; active program?
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain MOA losing favor; active program?
GP13269	Metabasis (Gensia)	adenosine kinase inhibitor	II	General pain, epilepsy
ZD4952	Zeneca	prostaglandin receptor antagonist	II	Moderate to severe pain
GV196771	Glaxo	glycine antagonist	II	Chronic pain

Sources: ADIS, IMS, company reports

Table 5. Development Pipeline – Nicotinic Mechanisms

Product	Company	Phase	Comment
GTS-21	Taiho	II	Target is Alzheimer's Disease May have preclinical pain program
SIB-1508Y	Sibia	II	Target is Parkinson's Disease Preclinical for dementia
SIB-1553A	Sibia	II	Target is Alzheimer's Disease
CMI 980	Cytomed	Preclinical	Target is pain Epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain
RJR 2557	Targacept (RJR)	Preclinical	Target is pain. Also for cognitive defects
Nicotinic agonists	Neurosearch	Preclinical	Target is pain

Sources: ADIS, IMS, company reports

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Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for other non-analgesic indications. The majority of the analgesic compounds in the pipeline represent incremental improvements to the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development are novel mechanisms with unique mechanisms of action. These novel mechanisms are expected to provide the bulk of the competition for ABT-594.

Among the novel agents in development, the greatest threat to ABT-594 is likely to be posed by other nicotinic compounds in development for pain. ABT-594, now in late Phase II trials, is likely probably the most advanced nicotinic compound in the analgesia pipeline. ABT-259, on the other hand, has a less substantial lead on other nicotinic compounds in development for pain. The first nicotinic compounds to be launched in the class may be for Alzheimer's Disease or Parkinson's Disease. These compounds do not represent a threat to ABT-594, unless significant safety concerns or evidence of tolerance, dependence or abuse are an issue and become associated with the class as a whole.

For the treatment of osteoarthritis (OA), the COX-2 inhibitors represent the most significant competition. The launch of Searle's Celebrex (celecoxib) in January 1999 is one of the most successful product launches in industry history. After ten weeks on the market, prescriptions for Celebrex represented 24% of new NSAID prescriptions. Merck's Vioxx (rofecoxib), approved in May 1999 is also expected to be a very successful product in the treatment of OA as well as other pain states.

The pipeline for the treatment of neuropathic pain does not have a blockbuster compound on the order of the COX-2 inhibitors. However, the follow-up to Parke-Davis' Neurontin (gabapentin) is expected to perform well. This compound, pregabalin, is significantly more potent than gabapentin which is expected to increase its efficacy while maintaining a relatively benign side effect profile.

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B.3 Unmet Needs

Unmet Need	Pipeline Impact
<ul style="list-style-type: none"> Efficacy in moderate to severe pain without tolerance, dependence or abuse 	<ul style="list-style-type: none"> Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities
<ul style="list-style-type: none"> Reduction in the GI adverse events profile of NSAIDs 	<ul style="list-style-type: none"> COX-2 inhibitors appear to reduce the incidence and severity of GI adverse events, but Celebrex retains labeled warnings regarding ulceration comparable to traditional NSAIDs COX-2s still demonstrate AEs at high dosage levels (small therapeutic window)
<ul style="list-style-type: none"> Overcome ceiling effect of NSAIDs 	<ul style="list-style-type: none"> More selective COX-2s (~1000 times more selective for COX-2 vs. COX-1) may allow higher dosing without incurring GI adverse events, thus overcoming current therapeutic ceiling Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594
<ul style="list-style-type: none"> Efficacy in neuropathic pain 	<ul style="list-style-type: none"> Pregabalin is expected to provide more significant relief of some types of neuropathic pain with fewer side effects than other adjuvant analgesics Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models
<ul style="list-style-type: none"> Few long-acting agents available for the treatment of acute pain 	<ul style="list-style-type: none"> Novel analgesics may have a longer duration of action than opioids

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance producing, non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe pain.

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B.4 ABT-594 Target Product Profile

Table 6. ABT-594 Target Profile

PPCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Indicated for the treatment of pain (general pain claim)	Indicated for the treatment of osteoarthritis pain	"General pain" claim not achievable due to slow onset of action; proof of principle established in molar extraction study	Medium	9/99, 1Q01	High
Effective in neuropathic pain	Indicated for the treatment of neuropathic pain	Indication specific claims now favored since general pain claim not achievable	Low	9/99, 2Q01	Medium
Effective for moderate to moderately-severe pain	N/A	No longer applicable without general pain claim	N/A	N/A	N/A
Not scheduled	No change	N/A	High	4Q02	High
Improved safety profile compared to opioids including: - less GI motility impairment - less respiratory depression - low tolerance potential - no dependence/withdrawal	No clinically significant tolerance, dependence or withdrawal	Simplify profile to focus on the most commercially important AEs	Medium	2Q01	High
	Very few abnormal LFTs	Abnormal LFTs in a few Phase I subjects	High	9/99	High
	Very low nausea/vomiting at effective dose	Relatively high incidence of nausea/vomiting in single dose Phase I & II subjects (food and dose dependent)	Medium	9/99	High
	Other safety OK	Simplify profile	Medium	9/99, 2Q01	High
	No significant or sustained differential efficacy in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	Low	9/99, 2Q01	High
	No significant or sustained differential side effect profile in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	High	9/99, 2Q01	Medium
	No re-initiation of cravings in ex-nicotine users	Possible due to nicotinic mechanism	Medium	2Q01	High

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Table 6. ABT-594 Target Profile (Continued)

PPCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Onset of action in less than 30 minutes	Onset of action comparable to other therapies used to treat OA	Onset of action estimated at 90 minutes in Phase II trial	Low	9/99	Medium
	Onset of action comparable to other therapies used to treat neuropathic pain	Onset of action estimated at 90 minutes in Phase II trial	High	9/99	Medium
BID/TID dosing	BID dosing	Competitive dynamics highlight importance of dosing convenience	High	9/99	Medium
No major drug interactions, especially with drugs used for common chronic conditions	No change	N/A	High	4Q00	Medium

B.5 Forecast

Table 7. U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rxs (MM)	280	285	291	297	303
- % chg	2%	2%	2%	2%	2%
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rxs (MM)	2.8	7.1	11.1	13.3	15.1
Price/Rx (\$)	34.97	35.67	36.39	37.12	37.86
Abbott Sales (\$MM)	125	254	402	495	573
R&D (\$MM)	5	5	4	4	3
SG&A (\$MM)	66	98	90	85	84
SMM (%)	97.2	97.3	97.3	97.4	97.4
Div. Margin (\$MM)	59	162	324	427	509

10 year pre-tax NPV @ 12.5% = \$1.016 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$587 MM

10 year post-tax ENVY @ 12.5% = TBD

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Key assumptions:

- Assumes 12/97 PPCC profile
- NDA Filed 12/01, Launch 6/03
- First in class ChCM
- Usage = 70% chronic and 30% acute
- Weighted average days per Rx = 15.6
- Stocking at 12% of first year's sales
- Detailing includes 30% of IMs, 25% of FPs and GPs, 25% of Rheumatologists, and 10% of Neurologists
- Sampling at 80% of details at launch, 8 units per detail, 5 days of therapy per unit
- Patent expires 12/2016

Forecast Update Plan:

Forecast will be updated in late June/early July 1999 to account for revised indications of OA and/or neuropathic pain and the associated spillover use in other pain states.
Forecast will be available well in advance of ABT-594 Go/No Go decision in 9/99.

Table 8. Ex-U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rxs (MM)	-	-	-	-	-
- % chg					
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rxs (MM)	-	-	-	-	-
Price/Rx (\$)	-	-	-	-	-
Abbott Sales (\$MM)	60	150	250	300	320
R&D (\$MM)	3.4	3.2	2.8	2.4	2.0
SG&A (\$MM)	27	53	50	48	45
SMM (%)	95%	95%	95%	95%	95%
Div. Margin (\$MM)	26	85	182	235	251

10 year pre-tax NPV @ 12.5% = \$428

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$253

10 year post-tax ENVY @ 12.5% = TBD

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Key assumptions:

- First in class ChCM
- Indicated for treatment of moderate to moderately-severe pain
- Effective in neuropathic pain
- Good tolerability and safety profile
- No nicotinic effects
- Launched in all AI regions, including Japan, simultaneously (2003)

Forecast Update Plan:

- Forecast will be updated 9/99 (in time for the Go/No Go decision) to reflect results of marketing research to be conducted 3Q 1999 regarding expected uptake of 594 in OA and neuropathic pain markets, as well as potential spill-over prescribing for other pain states.

Table 9. Global Forecast

	2003	2004	2005	2006	2007
U.S. Sales (\$MM)	125	254	402	495	573
Ex-U.S. Sales (\$MM)	60	150	250	300	320
Total Sales (\$MM)	185	404	652	795	893
Total Division Margin (\$MM)	85	247	506	662	760

10 year pre-tax NPV @ 12.5% = \$1.44 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$840 MM

10 year post-tax ENVY @ 12.5% = TBD

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C. MAJOR CHALLENGES AND STRATEGIES

C.1 Project History

Key Milestones	
Milestone	Date
PPCC Approval	12/96
Start Phase I	7/97
Start Phase II	7/98
First Phase II Result	12/98
GO/NO GO Efficacy*	9/99
Start Phase III	1/00
Regulatory Filings (US/EU)	12/01
Regulatory Approval	6/03

* Based on Phase II studies in molar extraction, osteoarthritis, and neuropathic pain.

- At PPCC, indications considered for ABT-594 were acute vs. chronic pain, with an acute pain claim being considered to have a shorter development course, as long term toxicology studies could theoretically be avoided with this approach.
- Input from FDA (3/98) indicated that if an oral dosage form was being pursued, i.e., the drug *could* be used long term (independent of indication being sought), then long term toxicology studies would be required.
- Decision analysis review of the program (3/98 - 7/98) arrived at several conclusions:
 - A general pain indication was preferred over filing for an acute indication earlier.
 - Carcinogenicity studies should be initiated prior to first Phase II results.
 - Development of follow-on compounds (in the same cholinergic channel modulator class and in different pharmacologic classes).

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- Data from the first Phase II study (single dose molar extraction) indicated that ABT-594's onset of action is 1.5 – 2 hours post dose. Because a general pain indication requires efficacy in acute pain states (with more rapid onset of action), ABT-594 was considered to be unlikely to achieve a general indication. The current clinical plan targets disease-specific indications.

The global target indications for ABT-594 are for the treatment of pain associated with osteoarthritis and for the treatment of neuropathic pain.

C.2 Registration

C.2.1 Indication

A major challenge to the development of ABT-594 is the identification of an optimal indication for this novel pharmacology. An understanding of the issues regarding indications for pain management requires a definition of terms.

Disease-specific Indication: The product would be indicated for pain management associated with specific disease or condition(s) such as osteoarthritis, diabetic neuropathy or dysmenorrhea.

General Indication: The product would be indicated for use in unspecified pain states (for the management of pain) without a limit on treatment duration.

Acute Indication: The product would be indicated for use in unspecified pain states, with duration of use of at most 5 days (typically, post-operative pain).

Historically at FDA, a typical submission has included approximately six efficacy studies (several single-dose dental pain studies, and several multiple dose orthopedic or post-operative pain studies) and safety studies. This package has resulted in a general pain indication.

While the FDA has regarded this approach as satisfactory given the broad analgesic efficacy of older compounds (NSAID's and opioids), newer pharmacologic approaches have created concerns at FDA that a drug studied for short periods may not be effective

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Collicott Deposition Exhibit 2

P's Exhibit BV Part 2

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in chronic pain states (e.g., low back pain, neuropathic pain). An FDA Advisory Committee meeting (March, 1998) recommended that acute studies should support *only* an acute indication, and chronic studies (in addition to acute studies) are required to support a general indication. The FDA indicated that it may use labels that distinguish compounds with efficacy in neuropathic pain from those without efficacy in this mechanistically distinct pain type. Currently no regulatory guidelines exist (FDA or EMEA) as to the requirements for a neuropathic pain indication. Carbamazepine (Tegretol, Novartis) is indicated for the management of trigeminal neuralgia, and topical lidocaine (Lidoderm, Endo) is indicated for the management of post-herpetic neuralgia.

Recent FDA/CPMP guidelines exist regarding disease-specific indications for osteoarthritis and rheumatoid arthritis and two COX-2 inhibitors have recently been approved by the FDA. Celebrex (celecoxib, Searle) is approved for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis. Vioxx (rofecoxib, Merck) is approved for the relief of signs and symptoms of osteoarthritis, dysmenorrhea (painful menstruation) and acute pain. A CPMP guideline recommends 6 month studies (vs. 3 months studies required by FDA) to support arthritis indications. For the EU there exists no precedent for a compound approved through the EMEA central filing procedure for a pain claim. Meetings to review our clinical trial strategy with worldwide regulatory authorities are planned to be scheduled after the GO/NO GO decision (9/1999).

Marketing research is ongoing to assess the commercial viability of the target indications: the treatment of pain associated with osteoarthritis and the treatment of neuropathic pain.

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C.2.2 Clinical/NPD

- Issue:** If ABT-594 is scheduled, the NPV is significantly reduced.
- Strategy:** An expert advisory meeting took place 11/98. The advisors felt it was unlikely that ABT-594 would be scheduled and recommended that we conduct several preclinical/clinical studies on the compound identified for Phase III development after the GO/NO GO (9/1999).

C.2.3 CMC

- Issue:** We are at risk for possible increases in the cost of drug substance because we are dependent on other vendors to manufacture ABT-594 drug substance.
- Strategy:** Abbott cannot manufacture highly potent compounds. CAPD has selected Chemsyn as the manufacturer of the bulk drug substance.

C.2.4 Toxicology

- Issue:** Six month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long term toxicology studies.
- Strategy:** No adenomas have been found in the study. Early deaths in the 2 year carcinogenicity study will be closely monitored. No further studies are recommended at this time.

C.2.5 Discovery

- Issue:** Given our leadership position in cholinergic channel modulator pharmacology, a critical program challenge is the establishment of milestones that optimize timing and decision-making for clinical development of follow-on compounds.
- Strategy:** ABT-259 was approved for Transition Team evaluation at DDC 9/98. An additional cholinergic channel modulator compound and an adenosine kinase inhibitor are currently targeted for DDC by 4Q 1999.

C.3 Price Setting and Reimbursement

Pricing trends in the U.S. market will remain relatively stable in the short term due to two factors. First, the effect of higher-priced branded products entering the market in each analgesic class is tempered by the loss of patent protection of other branded

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products, and the resulting price erosion due to generic competition. Secondly, the large size of the prescription pain market tends to absorb the impact of individual products' prices in each analgesic class. In the long term, however, the entry of several higher-priced novel analgesics may create an upward trend in prescription analgesic prices.

Due to the competitiveness of the pain management market, ABT-594 must favorably complete outcomes and pharmacoeconomic studies in order to gain significant formulary acceptance and use in managed care organizations (MCOs) and institutional settings. Marketing research and consultation with the PPD managed care department will help determine the appropriate number of studies, comparators and desired endpoints.

C.4 Commercial Issues and Opportunities

Issues

- ABT-594 must demonstrate an excellent safety profile for broad usage by general practitioners
 - Potential for AEs (nausea) still exists
 - Potential for addiction due to nicotinic mechanism still exists
- No DEA scheduling will be key to market success
- Implications, if any, of the differential side effects in smokers vs. non-smokers must be determined
- ABT-594 must demonstrate an advantage over COX-2s for the treatment of OA/RA pain in order to compete in this market
- Other novel analgesics (e.g., pregabalin, 2nd generation COX-2s) may beat ABT-594 to the market
- ABT-594 may face significant pricing pressures ex-US, given the large number of existing pain drugs, many of which are generic

Opportunities

- ABT-594 expected product profile would satisfy several significant unmet needs in the analgesia market
 - Avoids scheduling, addiction and tolerance issues of opioids while providing relief of moderate to severe pain

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- Overcomes ceiling effect of NSAIDs while offering equal or better safety profile
- Efficacious in neuropathic pain
- PPD primary market research and input from the European Pain Advisory indicate that physicians would embrace a drug with these attributes
- Although molar extraction studies indicate that ABT-594 is not appropriate for treatment of acute nociceptive pain, the total available market for ABT-594 is large
 - The osteoarthritis market is among the largest segments of the analgesia market
 - The neuropathic pain market is large and significantly underserved
 - A significant amount of "spillover prescribing" for other chronic pain states is likely
- ABT-594 is likely to be the first nicotinic acetylcholine receptor modulator, indicated for treatment of pain, to reach the market (other compounds with a nicotinic mechanism may launch before ABT-594, labeled for other indications such as Alzheimer's Disease or Parkinson's Disease)
- US market would likely support premium pricing for a novel analgesic offering advantages over currently available agents
- Potency of ABT-594 ensures low cost of goods

C.5 Patent Issues

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing generic coverage for ABT-594 and ABT-259 and a large class of structurally related analogs. The original filing date for this application dates back to October 9, 1992, and since this predates a 1996 change in patent law, we are afforded a choice of 20 years from date of filing or 17 years from date of issue, of which 17 years from issue provides the longer patent life. The anticipated expiration of patent coverage for composition of matter for ABT-594 and ABT-259 will be June, 2016. An additional application (6013.US.01), which includes species claims to ABT-594 and ABT-259 as well as use claims for the treatment of pain, was filed in December, 1996 and is pending. If this patent is allowed, it will provide 20 years from date of filing, which will extend the patent life of ABT-594 and ABT-259 to December, 2016.

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The original application providing generic composition of matter coverage was filed broadly ex. U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

Issue: We may have to pay for use of proprietary technology in preclinical development.

Strategy: A meeting was held at Abbott on 2/99 with representatives from SIBIA Neuroscience. SIBIA presented both on their technology platform and two compounds that are in early Phase II (SIB 1508Y) and Phase I (SIB 1553) development. An exclusive license for SIBIA's technology platform has been granted to Lilly, 5/99.

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D. CLINICAL TRIAL PROGRAM

D.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Given the spectrum of analgesic activity of ABT-594 in preclinical animal models of pain, the clinical development program for ABT-594 will evaluate the safety and efficacy of ABT-594 for the treatment of neuropathic pain and pain associated with osteoarthritis. In addition, pilot studies are planned to assess the safety and efficacy of ABT-594 for the treatment of pain associated with cancer.

Table 10. Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Indication (Study Type)	Phase II		Phase III		Phase IIIb	
	# Studies	# Patients	# Studies	# Patients	# Studies	# Patients
Osteoarthritis						
U.S.	1 ^c	250	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Neuropathic Pain						
U.S. ^a	1 ^c	150	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Cancer Pain						
U.S.	2	500	-	-	-	-
Long-Term Safety						
U.S.	-	-	1 ^a	600 ^d	-	-
Europe	-	-	1 ^a	300 ^d	-	-
Pricing Studies						
U.S.	-	-	-	-	1	500
Europe	-	-	-	-	1	500
Canada	-	-	-	-	1	500
Australia	-	-	-	-	1	500
TOTAL	4	900	12	5400	4	2000

a. Registration Trial

b. Bridging Study

c. Ongoing

d. Patients already counted in Phase III osteoarthritis and neuropathic pain studies.

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D.2 Registration Trials

Phase I

Seven Phase I studies have been completed with ABT-594. These initial Phase I studies have provided a preliminary determination of the pharmacokinetic, safety and tolerability profile of single and multiple dose administration of an oral liquid formulation of ABT-594 and the comparative bioavailability and effect of food on oral liquid and solid oral soft elastic capsule (SEC) and hard gelatin capsule (HGC) formulations.

Approximately 171 subjects have received at least one dose of ABT-594 (25 µg to 200 µg) as an oral solution under fasted (i.e., after a 10-hour fast) or fed conditions (i.e., approximately 30 minutes after a meal was served).

For the ABT-594 oral solution, dosing under fasted conditions was limited by vomiting after single dose administration at doses of 100 µg or higher; however, improved gastrointestinal (GI) tolerability was generally noted with continued dosing under fasted conditions and when ABT-594 was administered under fed conditions. The most frequently observed adverse events were dizziness, nausea, and vomiting. Most adverse events were mild in severity and occurred at doses of 100 µg or higher.

The pharmacokinetics of ABT-594 were linear at doses from 25 µg to 150 µg after single and multiple dose administration. No unexpected accumulation was observed after multiple dosing. Approximately 50% of an ABT-594 dose was recovered in urine. There was no effect of food on the C_{max} and AUC of ABT-594. The occurrence of adverse events of dizziness, nausea, and vomiting was significantly correlated with C_{max} , AUC, and dose.

Two Phase I studies (Study M97-706, Study M98-984) have assessed the bioavailability of ABT-594 oral solution, SEC, and HGC formulations. In Study M97-706 (n=22), the bioavailability of a single 100 µg dose of ABT-594 25 µg and 50 µg SEC formulations was shown to be equivalent to that of an ABT-594 oral solution formulation with regard to C_{max} and AUC. In Study M98-984 (n=23), based on preliminary analysis, the bioavailability of a single 100 µg dose of a 25 µg HGC formulation was similar to that of

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a 25 µg SEC formulation. In the same study, preliminary analysis also showed the pharmacokinetics of a single 150 µg ABT-594 dose to be similar for both the SEC and HGC formulations. In these studies, a single 100 µg dose of the SEC and HGC was well-tolerated with excellent GI tolerability (i.e., nausea, vomiting) under fasted conditions. For a single 150 µg dose, less vomiting was observed with the HGC and less nausea with the SEC under fasted conditions as compared to the oral solution in previous studies.

Eighteen additional Phase I studies are planned to be included in the registration package. These Phase I studies will be conducted so that data on specific drug interactions and pharmacokinetics and safety of ABT-594 in special populations can be included in the labeling and package insert once the product is approved. A table summarizing these studies is presented below:

Table 11. Summary of Planned Phase I Clinical Studies

Study	Number of Studies	Planned Number of Subjects	Anticipated Start Date
Bioavailability	3	72	4 Q '99
Human Metabolism	1	6	3 Q '99
Drug Interaction	6	192	1 Q '00
Special Populations:			
Renal Impairment	1	32	1 Q '00
Hepatic Impairment	1	32	
Smokers	1	48	
Geriatric	1	48	
Cardiovascular Safety	1	32	1 Q '00
Japanese Population:	3		
Single Rising Dose	1	60	1 Q '00
Food Effect	1	12	1 Q '00
Multiple Rising Dose	1	60	2 Q '00
Total Planned Phase I Studies:	18	594	

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Phase II

Five Phase II dose-ranging studies have been initiated. Two Phase II studies in dental pain following third molar extraction surgery (M97-772 and M97-897) used an ABT-594 oral liquid formulation have been completed. Two Phase II studies, one in neuropathic pain (n=150) and one in osteoarthritis (n=250) are currently ongoing. One study in post surgical pain was initiated but prematurely terminated due to the onset of active ABT-594.

The single dose molar extraction (M97-772) demonstrated that ABT-594 has analgesic effects with no differential effectiveness based on prior nicotine use, gender or baseline pain severity. However, these analgesic effects were associated with adverse events of nausea, vomiting and dizziness and a slow onset of action (1.5-2.0 hours). As a general pain claim is supported by evidence of acute efficacy, these results suggested that a general pain indication is unlikely to be achieved for ABT-594. The molar extraction model assessed the single dose safety and efficacy, dose response and onset of effect of ABT-594, but did *not* assess the multiple dose safety, efficacy, and durability of effect of ABT-594. These parameters are being assessed in the ongoing 3 week Phase II neuropathic pain (M98-833) and osteoarthritis (M98-826) studies.

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The five initiated Phase II dose-ranging trials are summarized in the following table:

Table 12. Summary of Ongoing and Completed Phase II Studies

Protocol No.	Study Description	ABT-594 Doses	Treatment Duration Regimen	Target Enrollment	Patients Enrolled	Status Conclusion
M97-772	Molar Extraction	25, 50, 75, or 100 µg	1 Day; QD	288	290	Completed; Efficacy seen at 100 µg dose; Onset at approximately 2 hours.
M97-897	Molar Extraction	100 µg	1 Day; QD	45	45	Completed; Efficacy not demonstrated; 90% of ABT-594 subjects received rescue medication prior to 2 hour analgesic onset.
M98-836	Post General Surgery	25, 50, or 75 µg	1 Day; QD	250	2	Study prematurely terminated due to slow onset of action of ABT-594 in M97-772
M98-833	Neuropathic Pain	25 or 75 µg	3 Weeks; BID	150	136	Study is ongoing
M98-826	Osteoarthritis	25, 50, 75 µg	3 Weeks; BID	250	256	Study is ongoing

Two Phase II pilot studies in patients with moderate to severe cancer pain are planned for the registration package. These studies are not aimed at an indication, but will be supportive studies to help establish favorable competitive position and regulatory approval. Each study will be a randomized, double-blind, placebo-controlled, morphine-sparing study of approximately 2 doses of ABT-594 in approximately 250 cancer patients.

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Go/No Go Decision:

A Go/No Go decision is planned for 9/99 based on the results of ongoing Phase II studies in neuropathic pain and osteoarthritis, and market research on disease specific claims (i.e., relief of signs with symptoms of neuropathic pain, or relief of signs and symptoms of osteoarthritis).

To support a Go decision for any indication, osteoarthritis (OA) and/or neuropathic pain (NP) Phase II studies should:

1. show trends such that Phase III studies will have 80% power to detect significant improvement associated with ABT-594 vs. placebo;
2. show acceptable safety;
3. show no clinical evidence for abuse liability.

For osteoarthritis, Phase II studies should also provide evidence that adequately powered Phase III studies would not show superiority of active control (e.g. ibuprofen) compared with ABT-594.

Phase III

The Phase III program is aimed at obtaining indications for the treatment of pain associated with osteoarthritis and neuropathic pain. The Phase III program in osteoarthritis and neuropathic pain will each consist of four 600 patient Phase III studies that will be conducted in the United States and Europe, and one 300 patient bridging study that will be conducted in Japanese subjects. Although a minimum of two pivotal studies are required for registration, this plan provides some back up should a study fail to meet its primary efficacy measure to statistical significance.

Each Phase III study will be a randomized, double-blind, placebo-controlled comparative study and will evaluate two doses of ABT-594. The duration of treatment for the Phase III osteoarthritis trials will range from 3 months to 6 months. The duration of treatment for the Phase III neuropathic pain studies will be approximately 3 months. Each Phase III program will enroll approximately 2400 patients and is designed to stand alone should one indication not show sufficient efficacy.

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In addition to these studies, two long-term, open-label safety studies are also planned for the registration package. One study will be conducted in the United States and the other will be conducted in Europe. The purpose of these trials will be to obtain the required long-term safety data on ABT-594. These studies will allow patients who have participated in any Phase III study conducted in the United States or Europe the option of receiving ABT-594 on a long-term basis. In addition, patients who never received ABT-594 who meet the inclusion criteria will be allowed to receive ABT-594 on a long term basis.

D.3 Trials Aimed at Enhancing Pricing and Reimbursement

Phase IIIb

Late Phase IIIb studies will be devoted to comparative studies using key analgesic competitors. Phase IIIb will examine issues of pricing, market penetration and pharmacoeconomics. Four Phase IIIb pricing studies are planned to be completed prior to market launch. These studies will not be completed at the time of NDA/EMEA submission. Each study will enroll approximately 500 patients. The location (country) in which these studies will be conducted will be selected to help obtain market penetration and obtain optimum pricing on a world-wide basis. At this time, it is anticipated that one study will be conducted in each of the following four countries: Australia, Canada, United States and Europe.

Phase IV

Phase IV studies will be planned once the results of Phase III studies are obtained and will be based upon the important analgesic competitors at the time of Phase IV trials.

D.4 Trials Aimed at Facilitating Launch and Market Penetration

Price determination, reimbursement status, product positioning, and product promotion will be critical for the commercial success of ABT-594. Given the recent market entry of COX-2 inhibitors, they will likely form much of the competition at the time ABT-594 is expected to launch. Phase IIIB outcomes and reimbursement studies in the U.S. and Europe are currently planned to start in 1Q01 and 2Q01, respectively. The specific tasks listed below are proposed to establish the market value of ABT-594:

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Quantification of the Health and Economic Burden of Chronic Pain (3Q'99)

1. Description of Practice Pattern Variation in Major Markets (4Q'99)
2. Development of a Decision-Analytic Model (4Q'99)
3. Preparation and Execution of a Phase III Piggyback Protocol (1Q'00)
 - Health-Related Quality of Life
 - Economics
4. Development and Execution of a Naturalistic Outcomes/Cost-Effectiveness Phase IIIB Trial (1Q'01)

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E. CHEMISTRY, FORMULATIONS, MANUFACTURING

E.1 CAPD

Process development remains on schedule to meet the commercial cost objective. Cost of goods was originally targeted to be \$0.125/day. This was based upon a 50 mg/day dosage. It now appears a dosage projection of less than 0.1 mg/day is more likely. Based upon this dosage scenario, it is expected a bulk drug substance cost of \$0.02/day can be achieved at launch. The target cost of drug substance at launch is \$2,500/kg.

ABT-594 bulk drug substance will be manufactured only at ChemSyn Laboratories in Harrisonville, Missouri. ChemSyn has been audited by CAPD supplier quality assurance group and approved as a supplier of bulk drugs. ChemSyn has recently completed construction of a new facility for the manufacture of highly potent drugs. This new facility is where they will manufacture registration batches for ABT-594 in August of 1999. The intermediate for ABT-594, BOC azetidine alcohol (BAA), will be manufactured only at Regis Technologies in Morton Grove, IL. Regis will be manufacturing their registration batches in May and June of 1999. As time allows, the process development team will optimize the process to manufacture the bulk drug substance in 1999. The development team will also work with the analytical support groups to set specifications on materials and intermediates used in the process and define the in-process testing required for control of the manufacturing process. All pertinent impurities will be identified and standards prepared to support analytical method development for CCM.

Bulk Drug Substance Cost Status

Bulk drug substance cost is expected to be \$20,000/Kg at the time of launch. Approximately 40% of the cost reflects manual charges. The balance of the costs includes labor and equipment, process support charges and supplier profit margin.

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Event	Year/Source	Cost/KG	Actual/Projected
DDCC	1996 / D-45L	\$200,000	Actual
	1997- CAPD	\$175,000	Actual
	1998- SICOR	\$40,000	Actual
NDA Lots	1999- CHEMSYN	\$29,000	Projected
NDA Filing	2001	\$29,000	Projected
Validation Lots	2002	\$20,000	Projected
Launch	2003	\$20,000	Projected

The projected cost of ABT-594 bulk drug substance at launch (6/03) that was established during PPCC (12/96) was \$2,500.00/kg. The current projected cost of bulk drug substance at the time of launch is projected to be \$20,000.00/kg

The projected average daily dose is expected to be approximately 200 µg/day. Based upon a dosage projection of 0.2 mg, it is expected that the cost of drug substance at launch will be approximately \$0.004 per day.

ABT-594 Bulk Drug Substance Requirements

Project: G02Q143-010

End Q4 1999

Inventory Balance
15 kg

Bulk Deliveries			Usage (Quantity)			
	Description	Quantity	Clinical	Formulation	Scale-Up	Inventory
Q1 2000			0.5 kg	0.5 kg		14.0 kg
Q2 2000				0.5 kg	9.0 kg	4.5 kg
Q3 2000					3.0 kg	1.5 kg
Q4 2000						
Q1 2001						
Q2 2001						
Q3 2001						
Q4 2001	Validation Lots (n-3)	15 kg			3.0 kg	13.5 kg

Lead Time (request to delivery; weeks) 8

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E.2 PARD

Clinical Formulations: Rising dose safety and molar extraction studies were performed using a solution formulation. Phase II studies in osteoarthritis and neuropathic pain are underway using a softgel capsule formulation (SEC). The softgel formulation was shown to delay T_{max} , therefore, a rapidly dissolving hard gelatin capsule (HGC) formulation has been developed as the target Phase III formulation. A 25 mcg HGC is currently in a biostudy vs. SEC. A 75 mcg HGC will be tested for bioavailability 6/99.

Commercial Formulation: Primary candidate for commercial formulation is HGC at dosage strength(s) to be determined by results of Phase II studies.

Formulation-Dependent Absorption Rate: If therapeutic onset is too slow with oral solution and capsule formulations, sublingual dosing may provide more rapid absorption. To this end, clinical supplies of "Zydis" instantly disintegrating tablets have been manufactured. Rapidly disintegrating conventional tablets are also possible, avoiding royalty and manufacturing payments to Schere DDS. Biostudy with sublingual dosing is on hold.

Key Issues: Formulation and processing alternatives are limited by three factors: (1) content uniformity challenges due to low dose, (2) incompatibility with many commonly used excipients, and (3) low allowable employee exposure limits. The HGC formulas under development address factors (1) and (2). Factor (3) will require capital investment at PPD's Abbott Park or Puerto Rico manufacturing facilities, or manufacture by a third party (TPM). Preliminary evaluation of facilities modifications has been done; preliminary evaluation of TPMs has occurred as a result of other projects.

Critical Path Activities: Formulation scale-up is expected to occur 2Q00; NDA stability lots are expected to be manufactured 3Q00. 1 year stability results are expected to be available 9/01 in support of the 12/1/01 FDA/EMEA submissions.

IV Formulation: Parenteral formulation is on hold. It is expected that a lyophilized formulation will be required. Clinical supplies may be available 6 months post-funding.

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E.3 Manufacturing

The primary manufacturing sites in consideration are API, AP16 and RP Scherer. API Potent Drug Module would produce hard gelatin powder filled capsules. This process utilizes the 600L TK Fielder granulator, vacuum V-Blender, a potential milling step and encapsulation. AP16 Microwave Gral process would also produce hard gelatin powder filled capsules. This process involves the 300L microwave granulator, Bin blending and encapsulation. RP Scherer would produce softgel capsules. This process includes a Hicks Reactor, a vessel to reduce particle size and softgel capsulation. The granulation process demonstrated excellent stability and dissolution properties. However, both the API and AP16 options require significant capital. The RP Scherer formulation is doable but is sending the business outside. We are gathering detailed information on cost estimates for each manufacturing option. Manufacturing options are constrained by extremely low employee exposure limit (EEL) of 1 ug/m^3 .

Timeline for manufacturing include the following: 1) Phase III supplies starting 9/1999, 2) Identification of manufacturing site 9/1999, 3) Upgrade of Abbott site if necessary starting 9/1999, 4) Go/No-Go decision 9/1999, 5) Prescale up runs 2nd Qtr/2000 and 6) Regulatory scaleup runs starting 2nd Qtr/2000.

Manufacturing cost for bulk drug is \$2,500/kg. Finished product will be determined by the site selection. The dosage strength is still to be determined but is estimated to be 100 ug or less. Cost estimates for ABT-594 have not been completed.

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F. NON-CLINICAL

F.1 Toxicology

Relative to therapeutically efficacious doses in rats, ABT-594 has proven to be a relatively non-toxic product, aside from its emetic liability in monkeys. One-month toxicity studies in rat and monkey, three-month studies in rat, mouse and monkey, and six-month study in rat have been completed. A 12-month monkey study, and rat and mouse carcinogenicity studies are ongoing.

In rats, reduced body weights and food intake were observed at all dosages tested; these changes were judged likely to be due to a pharmacologic effect of the compound. Treatment-related findings in rat studies included increased bile acids, hematologic alterations, increased ALT and liver weights changes. In the six-month study, basophilic foci of cellular alteration were noted in livers of 1/20, 3/20 and 5/20 female animals from the 0.2, 0.5 and 2.0 mg base/kg/day dosage groups, respectively. The presence of foci of cellular alteration in rat livers is frequently related to the administration of carcinogenic compounds, but foci are by definition not neoplastic, and some types (e.g., the tigroid type seen in this study) are disputed as not truly representing preneoplastic lesions. They are regarded as proliferative, however, and a relationship to drug treatment suggests some sort of stimulus to cell replication. Any further works to investigate the mechanism of this liver finding will wait until the go/no go decision is made.

In monkeys, emesis and abnormal stool were seen; these were regarded as pharmacologic effects of this class of compound. Other drug-related effects included clinical signs and changes in hematology, serum chemistry, organ weights and histopathology. These findings were consistent with dehydration and exacerbation of a non-specific stress-related response.

A fertility and general reproduction study in rat, and teratogenicity studies in rat and rabbit have also been completed. There were no adverse effects on reproduction or embryo/fetal development. A peri- and postnatal study of ABT-594 in rat is currently ongoing. A juvenile rat study is schedule to start during the first quarter of 2001.

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Genetic toxicology studies conducted with ABT-594 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-594 was not found to be genotoxic in any of these assays. However, a mesylate impurity in the finished product was found to be weakly mutagenic in a single strain of bacteria (TA1535) in the Ames test. There are ongoing efforts in determining and setting safe limits of this impurity in future bulk drug lots.

All toxicology studies needed for the go/no go decision have been completed. As mentioned earlier, the only toxicology issue with ABT-594 at this time is the finding of basophilic foci in the rat liver. This finding should have no impact on labeling or milestone dates. The carcinogenicity studies are scheduled to be completed during the fourth quarter of 2001. If the findings in these studies are negative, no further toxicology work will be necessary and the milestone date of 12/01 for NDA filing should be met.

F.2 Metabolism

Animal ADME studies (mouse, rat and monkey) have shown that oral doses of tritiated ABT-594 drug are well absorbed, not extensively metabolized and excreted into the urine primarily as unchanged parent drug. The major biotransformation products have been identified and include oxidative and conjugated metabolites. *In vitro* studies with cDNA-expressed human cytochrome P450 (CYP) isoforms suggested that CYP2D6 could slowly catalyze the oxidative metabolism of ABT-594. However, the contribution of CYP2D6 to the total elimination of the drug is likely to be very small, suggesting that coadministered drugs which induce or inhibit CYP-dependent metabolism are not likely to alter the clearance of ABT-594 in humans. Other *in vitro* experiments showed that ABT-594 did not adversely inhibit the metabolism of a number of CYP selective substrates by human liver microsomes, suggesting little potential for clinically relevant drug/drug interactions. Studies in one or more species have shown that ABT-594 is not highly bound to plasma proteins and is uniformly distributed in human whole blood. Total radioactivity is widely distributed throughout rat tissues and demonstrated an affinity to bind to melanin containing tissues in pigmented rats.

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Placental and lacteal transfer studies of the radiolabeled drug in rats are scheduled to begin in the fourth quarter of 1999 or early in 2000. A limited tissue distribution study in pigmented rats is also planned to determine the half-life of total radioactivity in melanin-containing tissues. A radiolabeled study in normal human subjects is scheduled for 2000.

F.3 Animal Pharmacology

The only animal pharmacology study ongoing that may be required later in the development of ABT-594 is a migraine study in Professor Peter Goadsby's Laboratory, Institute of Neurology, London. A report is anticipated in the 3rd quarter of 1999 on the effects of ABT-594 in a cat model of migraine.

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G. DEVELOPMENT COST AND SENSITIVITY ANALYSIS

The development milestones for ABT-594 are as follows:

Milestones	Date
PPCC Approval	12/96
Start Funding	1/97
Go/No Go Preclinical Safety	6/97
Start Phase I Europe	7/97
File IND (Liquid)	2/98
Start Phase II U.S.	7/98
Go/No Go Clinical Efficacy	9/99
File CTX/CTN	10/99
End of Phase II Mtg. w/FDA	11/99
Start Phase III U.S./Europe	12/99
Start Phase I Japan	2/00
Start Phase III Bridging Japan	1/01
File Europe - EMEA	12/01
File U.S. NDA - FDA	12/01
File Japan - Koseisho	6/02
Regulatory Approval U.S.	6/03

G.1 Base Case Scenario

The base case scenario consists of pursuing both the neuropathic pain and osteoarthritis indications. The Phase III program is aimed at obtaining indications for the treatment of pain associated with osteoarthritis and neuropathic pain. The Phase III program for osteoarthritis and neuropathic pain will each consist of three 600 patient Phase III pivotal studies to be conducted in the United States and one 600 Phase III study to be conducted in Europe to help facilitate regulatory approval and pricing in Europe. One 300 patient bridging study for each indication is also planned to be conducted in Japanese subjects.

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Planned Phase II and III Studies:

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	5	2700
Neuropathic Pain	1	150	5	2700
Cancer Pain	2	500	N/A	N/A
TOTAL	4	900	10	5400

* Does not include 2 long-term safety studies but does include Japan bridging studies.

Cost Through the NDA:

YEAR	COST
1999	29.9
2000	93.2
2001	50.5
TOTAL COST TO NDA	173.6

Breakdown by Year and Department:

	9/99 (to Go/NoGo)	1999	2000	2001 (to NDA)
PARD & CAPD	5.2	6.5	8.0	8.0
Drug Safety	3.8	4.7	5.0	2.5
Stats & DM	1.3	1.8	9.0	10.0
Venture Mgt	5.9	8.4	12.0	11.0
Grants	3.6	6.5	55.7	16.0
Other	1.8	2.0	3.5	3.0
TOTAL	21.6	29.9	93.2	50.5

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Breakdown by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEOARTHRITIS	TOTAL
1999	20.9	0	9.0	29.9
2000	36.9	29.2	27.1	93.2
2001	43.3	6.0	1.2	50.5
TOTAL	101.1	35.2	37.3	173.6

G.2 Downside Scenario (Funding Decrease)

Should funding need to be decreased, the strategy would be to eliminate one Phase III pivotal study from each indication. The negative aspect of this strategy adds more risk to the program, should one of the remaining two studies not statistically meet its efficacy outcome goal. The downside scenario is summarized in the following tables:

Downside Scenario Of Planned Phase II and III Studies

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	4	2100
Neuropathic Pain	1	150	4	2100
Cancer Pain	2	500	n/a	n/a
TOTAL	4	900	8	4200

Cost of Downside Scenario Through the NDA:

YEAR	COST
1999	27.7
2000	78.6
2001	54.4
TOTAL COST TO NDA	160.7

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Breakdown of Downside Scenario by Key Milestones and Department:

	9/99 (to Go/No Go)	1999	2000	2001 (to NDA)
PARD & CAPD	5.2	6.3	7.8	7.8
Drug Safety	3.8	4.7	5.0	2.5
Stats & DM	1.3	1.6	8.0	9.5
Venture Mgt	5.9	8.0	11.0	10.5
Grants	3.6	7.5	49.0	15.2
Other	1.8	1.8	3.5	3.0
TOTAL	21.6	27.9	84.3	48.5

Breakdown of Downside Scenario by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEOARTHRITIS	TOTAL
1999	20.9	0	7.0	27.9
2000	36.9	25.2	22.2	84.3
2001	43.3	4.0	1.2	48.5
TOTAL	101.1	29.2	30.4	160.7

G.3 Upside Scenario (Funding Increase)

The development strategy should additional funding become available would be to pursue an indication for the treatment of cancer pain. Three 600 patient Phase III pivotal studies would be planned for the U.S. and one would be planned for Europe.

A summary of the upside scenario is presented in the following tables:

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Upside Scenario of Planned Phase II and III Studies:

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	5	2700
Neuropathic Pain	1	150	5	2700
Cancer Pain	2	500	5	2700

Cost of Upside Scenario Through the NDA:

YEAR	COST
1999	29.9
2000	93.2
2001	69.0
2002	16.8
TOTAL COST TO NDA	208.9

Breakdown of Upside Scenario by Key Milestones and Department:

	9/99 (to Go/NoGo)	1999	2000	2001 (to NDA)	2002 (to SNDA)
PARD & CAPD	5.2	6.5	8.0	8.0	0.5
Drug Safety	3.8	4.7	5.0	2.5	0
Stats & DM	1.3	1.8	9.0	10.0	2.0
Venture Mgt	5.9	8.4	12.0	11.0	2.0
Grants	3.6	6.5	55.7	34.5	11.3
Other	1.8	2.0	3.5	3.0	1.0
TOTAL	21.6	29.9	93.2	69.0	16.8

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Breakdown of Upside Scenario by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEO-ARTHRITIS	CANCER PAIN	TOTAL
1999	20.9	0	9.0	0	29.9
2000	36.9	29.2	27.1	0	93.2
2001	43.0	6.0	1.2	18.5	69.0
2002	0	0	0	16.8	16.8
TOTAL	101.1	35.2	37.3	35.3	208.9

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Project Summary by Dept.

06/17/99

Analgesia

Project ABT-594

Version Plan

Sponsor All

Indication Pain (General)

Formulation Oral Solid

Dept. Advanced Technology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 10,657	\$ 42,912	\$ 53,569
1997	\$ 235,263	\$ 250,205	\$ 491,455	\$ 598,745	\$ 1,575,670
1998	\$ 168,935	\$ 167,725	\$ 175,046	\$ 165,493	\$ 677,200
1999	\$ 166,156	\$ 162,461	\$ 161,738	\$ 159,917	\$ 650,273
2000	\$ 146,079	\$ 146,079	\$ 111,761	\$ 99,792	\$ 503,714
2001	\$ 493,585	\$ 223,384	\$ 43,140	\$ 15,976	\$ 776,087
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Analytical Departments

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 483,095	\$ 232,800	\$ 273,694	\$ 870,408	\$ 1,859,998
1998	\$ 439,774	\$ 1,052,472	\$ 609,632	\$ 341,846	\$ 2,443,725
1999	\$ 378,395	\$ 171,735	\$ 561,971	\$ 238,276	\$ 1,350,379
2000	\$ 304,339	\$ 159,215	\$ 73,450	\$ 65,257	\$ 602,262
2001	\$ 718,730	\$ 354,731	\$ 176,462	\$ 63,471	\$ 1,313,395
2002	\$ 120,694	\$ 122,035	\$ 123,376	\$ 123,376	\$ 489,484
2003	\$ 120,694	\$ 116,588	\$ 23,152	\$ 23,152	\$ 283,588
2004	\$ 22,900	\$ 21,294	\$ 10,215	\$	\$ 54,410

Dept. Analytical Development

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 407,076	\$ 80,086	\$ 169,094	\$ 544,254	\$ 1,200,512
1998	\$ 323,136	\$ 526,208	\$ 269,145	\$ 282,787	\$ 1,401,279
1999	\$ 501,870	\$ 513,551	\$ 609,296	\$ 125,345	\$ 1,750,064
2000	\$	\$	\$	\$	\$
2001	\$	\$	\$	\$ 1,048,834	\$ 1,048,834
2002	\$ 95,403	\$	\$	\$	\$ 95,403
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

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ABBT 0019051

Project summary continues ...

Dept. Animal Services

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 4,750	\$ 8,727	\$ 13,477
1997	\$ 22,815	\$ 97,671	\$ 164,209	\$ 106,901	\$ 391,599
1998	\$ 34,635	\$ 160,359	\$ 217,042	\$ 251,239	\$ 663,275
1999	\$ 130,181	\$ 121,848	\$ 98,343	\$ 89,769	\$ 440,143
2000	\$ 88,793	\$ 88,793	\$ 82,362	\$ 29,879	\$ 289,828
2001	\$	\$	\$	\$	\$
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. CAPD

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 752,697	\$ 94,691	\$ 270,305	\$ 1,154,305	\$ 2,272,000
1998	\$ 1,024,705	\$ 1,189,996	\$ 582,495	\$ 582,495	\$ 3,379,692
1999	\$ 1,751,028	\$ 627,279	\$ 714,672	\$ 221,327	\$ 3,314,307
2000	\$	\$	\$	\$	\$
2001	\$	\$	\$	\$ 6,520,989	\$ 6,520,989
2002	\$ 593,010	\$	\$	\$	\$ 593,010
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. CCM - Pain Management

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$	\$ 22,874	\$ 1,428,470	\$ 1,011,771	\$ 2,463,116
1998	\$ 134,510	\$ 671,568	\$ 2,437,072	\$ 1,811,126	\$ 5,054,278
1999	\$ 1,930,518	\$ 2,079,560	\$ 1,955,284	\$ 9,995,221	\$ 15,960,585
2000	\$ 14,055,072	\$ 20,758,630	\$ 20,770,536	\$ 20,181,969	\$ 75,766,207
2001	\$ 11,133,093	\$ 6,873,167	\$ 7,064,646	\$ 3,255,536	\$ 28,326,443
2002	\$ 559,905	\$ 402,769	\$ 382,479	\$ 382,479	\$ 1,727,633
2003	\$ 374,164	\$ 378,321	\$ 18,687	\$ 41,284	\$ 812,458
2004	\$	\$	\$	\$	\$

Dept. Clinical Packaging

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$	\$ 42,205	\$ 51,786	\$ 7,984	\$ 101,976
1998	\$ 1,041	\$ 148,437	\$ 213,028	\$ 76,259	\$ 438,766
1999	\$ 59,747	\$ 96,049	\$ 25,686	\$ 570,825	\$ 752,309
2000	\$ 702,160	\$ 436,549	\$ 381,020	\$ 269,264	\$ 1,788,994
2001	\$ 238,371	\$ 90,440	\$ 88,339	\$ 49,013	\$ 466,165
2002	\$ 6,254	\$ 6,324	\$ 6,393	\$ 6,393	\$ 25,366
2003	\$ 6,254	\$ 6,324	\$ 69	\$	\$ 12,648
2004	\$	\$	\$	\$	\$

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ABBT 0019052

Project summary continues ...

Dept. Data Mgmt

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 10,482	\$ 10,482
1997	\$ 11,122	\$ 49,418	\$ 118,915	\$ 118,489	\$ 297,946
1998	\$ 92,007	\$ 129,467	\$ 490,658	\$ 431,918	\$ 1,144,052
1999	\$ 154,737	\$ 179,015	\$ 387,325	\$ 512,108	\$ 1,233,185
2000	\$ 1,393,065	\$ 1,949,078	\$ 1,820,484	\$ 2,246,111	\$ 7,408,740
2001	\$ 2,877,738	\$ 1,303,668	\$ 945,111	\$ 1,568,880	\$ 6,695,399
2002	\$ 323,891	\$ 63,448	\$ 56,784	\$ 56,784	\$ 500,910
2003	\$ 55,550	\$ 56,167	\$ 491,653	\$ 12,295	\$ 615,667
2004	\$	\$	\$	\$	\$

Dept. Drug Analysis

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 96,583	\$ 58,121	\$ 102,414	\$ 176,405	\$ 433,525
1998	\$ 115,928	\$ 110,053	\$ 182,340	\$ 133,862	\$ 542,185
1999	\$ 93,699	\$ 126,122	\$ 138,102	\$ 100,533	\$ 458,457
2000	\$ 130,094	\$ 547,815	\$ 577,273	\$ 370,042	\$ 1,625,226
2001	\$ 205,567	\$ 75,677	\$ 10,085	\$ 4,805	\$ 296,136
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Formulation Departments

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 117,100	\$ 149,552	\$ 78,811	\$ 218,372	\$ 563,836
1998	\$ 161,127	\$ 280,924	\$ 269,205	\$ 167,706	\$ 878,963
1999	\$ 158,945	\$ 160,711	\$ 131,809	\$ 238,162	\$ 689,628
2000	\$ 408,672	\$ 157,660	\$ 33,808	\$ 33,808	\$ 633,949
2001	\$ 28,288	\$ 90,896	\$ 103,518	\$ 71,467	\$ 294,171
2002	\$ 26,962	\$ 27,262	\$ 27,561	\$ 27,561	\$ 109,347
2003	\$ 26,962	\$ 25,764	\$	\$	\$ 52,726
2004	\$	\$	\$	\$	\$

Dept. Formulation Development

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 117,100	\$ 149,552	\$ 78,811	\$ 218,372	\$ 563,836
1998	\$ 161,127	\$ 280,924	\$ 269,205	\$ 167,706	\$ 878,963
1999	\$ 158,945	\$ 160,711	\$ 131,809	\$ 238,162	\$ 689,628
2000	\$ 408,672	\$ 605,963	\$ 289,626	\$ 44,067	\$ 1,348,330
2001	\$ 38,324	\$ 90,034	\$ 89,016	\$ 71,467	\$ 288,842
2002	\$ 420,572	\$ 577,286	\$ 37,463	\$ 37,463	\$ 1,072,786
2003	\$ 36,648	\$ 35,558	\$	\$	\$ 72,207
2004	\$	\$	\$	\$	\$

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ABBT 0019053

Project summary continues ...

Dept. Integrative Pharmacology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 96,288	\$ 95,954	\$ 95,604	\$ 56,721	\$ 344,569
1998	\$ 11,369	\$ 11,495	\$ 11,622	\$ 11,116	\$ 45,604
1999	\$ 11,369	\$ 11,495	\$ 11,622	\$ 11,116	\$ 45,604
2000	\$ 11,338	\$ 11,338	\$ 11,463	\$ 11,463	\$ 45,604
2001	\$	\$	\$	\$	\$
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Metabolism

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 59,225	\$ 59,225
1997	\$ 201,936	\$ 152,297	\$ 100,463	\$ 178,873	\$ 633,571
1998	\$ 234,032	\$ 152,999	\$ 139,676	\$ 80,553	\$ 607,262
1999	\$ 59,016	\$ 36,075	\$ 133,191	\$ 90,445	\$ 318,729
2000	\$ 87,821	\$ 72,865	\$ 39,932	\$ 13,147	\$ 213,767
2001	\$ 48,662	\$ 21,340	\$ 3,361	\$ 1,601	\$ 74,966
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. PARD Management

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
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..... No Data for This Combination

Dept. Pathology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 9,228	\$ 75,235	\$ 84,463
1997	\$ 135,807	\$ 182,025	\$ 166,772	\$ 94,872	\$ 579,478
1998	\$ 129,052	\$ 77,012	\$ 64,790	\$ 68,506	\$ 339,361
1999	\$ 120,131	\$ 52,991	\$ 70,993	\$ 74,932	\$ 319,048
2000	\$ 22,538	\$ 21,648	\$ 20,080	\$ 104,938	\$ 169,205
2001	\$ 226,892	\$ 290,092	\$ 264,241	\$	\$ 781,226
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

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ABBT 0019054

Project summary continues ...

Dept. Pharm Analysis & Stability

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 67,284	\$ 111,476	\$ 65,784	\$ 113,926	\$ 358,472
1998	\$ 73,488	\$ 506,763	\$ 352,189	\$ 95,480	\$ 1,027,922
1999	\$ 91,079	\$ 92,091	\$ 98,748	\$ 162,134	\$ 444,054
2000	\$ 260,237	\$ 375,294	\$ 181,892	\$ 57,453	\$ 874,878
2001	\$ 602,346	\$ 262,531	\$ 63,422	\$ 44,310	\$ 972,611
2002	\$ 334,426	\$ 274,134	\$ 125,434	\$ 125,434	\$ 859,429
2003	\$ 122,707	\$ 118,623	\$ 3,991	\$ 3,991	\$ 249,314
2004	\$ 3,948	\$ 3,145	\$ 768	\$	\$ 7,862

Dept. PK/Biopharmaceutics

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1998	\$ 3,502	\$ 6,128	\$ 12,947	\$ 37,924	\$ 60,503
1999	\$ 49,153	\$ 49,487	\$ 44,945	\$ 37,292	\$ 180,879
2000	\$ 15,091	\$ 110,013	\$ 204,028	\$ 148,536	\$ 477,669
2001	\$ 31,910	\$ 7,771	\$	\$	\$ 39,682
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Process Development

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
------	-------------	-------------	-------------	-------------	--------

..... No Data for This Combination

Dept. R&D Records Center

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 370	\$ 370
1997	\$ 7,090	\$ 7,618	\$ 9,609	\$ 9,541	\$ 33,860
1998	\$ 9,473	\$ 22,765	\$ 54,322	\$ 51,595	\$ 138,156
1999	\$ 50,081	\$ 51,206	\$ 52,949	\$ 39,970	\$ 194,207
2000	\$ 46,494	\$ 49,209	\$ 49,231	\$ 44,177	\$ 189,112
2001	\$ 35,891	\$ 38,918	\$ 17,601	\$ 4,696	\$ 97,108
2002	\$ 17,325	\$ 15,951	\$ 15,646	\$ 15,646	\$ 64,569
2003	\$ 15,306	\$ 15,476	\$ 283	\$ 801	\$ 31,868
2004	\$	\$	\$	\$	\$

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ABBT 0019055

Project summary continues ...

Dept. Regulatory Affairs

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 8,539	\$ 8,634	\$ 603	\$ 508	\$ 18,285
1998	\$ 497	\$ 5,821	\$ 16,819	\$ 16,819	\$ 39,958
1999	\$ 16,454	\$ 16,636	\$ 16,819	\$ 24,010	\$ 73,921
2000	\$ 23,749	\$ 23,749	\$ 24,010	\$ 23,844	\$ 95,353
2001	\$ 22,991	\$ 28,877	\$ 352,029	\$ 352,883	\$ 756,782
2002	\$ 20,704	\$ 366,310	\$ 21,164	\$ 21,164	\$ 429,342
2003	\$ 20,704	\$ 20,934	\$	\$	\$ 41,638
2004	\$	\$	\$	\$	\$

Dept. Res Services/Planning

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 34,031	\$ 34,410	\$ 1,958	\$ 1,580	\$ 71,980
1998	\$ 1,545	\$ 3,187	\$ 6,561	\$ 6,561	\$ 17,857
1999	\$ 6,419	\$ 6,490	\$ 6,561	\$ 5,169	\$ 24,640
2000	\$ 5,112	\$ 5,112	\$ 5,169	\$ 4,653	\$ 20,048
2001	\$ 3,510	\$ 3,549	\$ 1,443	\$ 796	\$ 9,300
2002	\$ 4,215	\$ 4,262	\$ 4,309	\$ 4,309	\$ 17,096
2003	\$ 4,215	\$ 4,262	\$	\$	\$ 8,478
2004	\$	\$	\$	\$	\$

Dept. Research QA

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 4,135	\$ 4,135
1997	\$ 12,927	\$ 32,632	\$ 21,416	\$ 20,834	\$ 87,811
1998	\$ 33,356	\$ 26,304	\$ 14,844	\$ 32,379	\$ 106,885
1999	\$ 59,688	\$ 38,634	\$ 39,224	\$ 58,548	\$ 196,096
2000	\$ 81,622	\$ 144,534	\$ 170,128	\$ 176,115	\$ 572,399
2001	\$ 117,854	\$ 119,325	\$ 117,045	\$ 361,617	\$ 715,842
2002	\$ 27,202	\$ 178,063	\$ 846	\$ 846	\$ 206,959
2003	\$ 828	\$ 837	\$	\$	\$ 1,665
2004	\$	\$	\$	\$	\$

Dept. Statistics

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$	\$ 2,084	\$ 5,272	\$ 6,647	\$ 14,004
1998	\$ 7,491	\$ 19,765	\$ 51,998	\$ 71,949	\$ 151,204
1999	\$ 60,239	\$ 72,090	\$ 89,504	\$ 137,008	\$ 358,843
2000	\$ 151,519	\$ 252,420	\$ 315,189	\$ 206,279	\$ 925,408
2001	\$ 227,941	\$ 330,952	\$ 43,362	\$ 187,602	\$ 789,859
2002	\$ 228,378	\$ 42,221	\$ 4,792	\$ 4,792	\$ 280,185
2003	\$ 4,688	\$ 4,740	\$ 29,062	\$ 41,966	\$ 80,458
2004	\$	\$	\$	\$	\$

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ABBT 0019056

Project summary continues ...

Dept. Statistics - Pre-Clinical

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 5,297	\$ 23,624	\$ 28,921
1997	\$ 71,773	\$ 17,663	\$ 9,517	\$ 35,345	\$ 134,300
1998	\$ 64,175	\$ 36,290	\$ 14,459	\$ 13,835	\$ 128,762
1999	\$ 16,651	\$ 8,757	\$ 10,622	\$ 10,311	\$ 46,342
2000	\$	\$	\$	\$ 6,592	\$ 6,592
2001	\$ 15,316	\$ 19,583	\$ 17,838	\$	\$ 52,738
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Toxicology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 30,760	\$ 64,068	\$ 94,828
1997	\$ 235,198	\$ 190,468	\$ 327,670	\$ 309,600	\$ 1,062,937
1998	\$ 194,431	\$ 230,326	\$ 414,177	\$ 379,115	\$ 1,218,050
1999	\$ 329,377	\$ 214,823	\$ 183,067	\$ 173,756	\$ 901,024
2000	\$ 137,780	\$ 134,218	\$ 124,496	\$ 64,696	\$ 461,192
2001	\$ 45,378	\$ 58,018	\$ 52,848	\$	\$ 156,245
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

by Department Project Totals

View Total Cost

Sponsor All

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Grand Totals
1996	\$	\$	\$ 60,694	\$ 288,781	\$ 349,475
1997	\$ 3,113,735	\$ 2,062,447	\$ 4,032,642	\$ 5,854,464	\$ 15,063,290
1998	\$ 3,419,347	\$ 5,817,001	\$ 6,869,283	\$ 5,278,281	\$ 21,383,914
1999	\$ 6,353,889	\$ 5,049,829	\$ 5,674,293	\$ 13,314,345	\$ 30,392,357
2000	\$ 18,480,257	\$ 26,050,190	\$ 25,285,946	\$ 24,202,091	\$ 94,018,486
2001	\$ 17,112,397	\$ 10,282,961	\$ 9,453,516	\$ 13,623,953	\$ 50,472,828
2002	\$ 2,778,949	\$ 2,080,071	\$ 806,253	\$ 806,253	\$ 6,471,526
2003	\$ 788,725	\$ 783,599	\$ 566,901	\$ 123,492	\$ 2,262,719
2004	\$ 26,849	\$ 24,439	\$ 10,984	\$	\$ 62,272

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ABBT 0019057

Project Assumption Report

Report As Of: Jun 17, 199

Project Number

G0 143010

Project Name

ABT-594

Active

Phase: 0

Activity	Protocol	Activity Start	Activity End	No. Patients	No. Sites	Manpower PMP	Manpower IMP	Direct Dollars	Grant Dollars	Comments
Prepare ISS/ISE		Apr 1, 2001	Sep 15, 2001	0	0					
NDA Preparation		Jul 1, 2001	Nov 29, 2001	0	0					
NDA Filing		Dec 1, 2001	Dec 1, 2001	0	0					

Active

Phase: 1

Activity	Protocol	Activity Start	Activity End	No. Patients	No. Sites	Manpower PMP	Manpower IMP	Direct Dollars	Grant Dollars	Comments
Ph I Single Dose (M97-676)	M97676	Jul 1, 1997	Sep 15, 1997	80	1 England					
Ph I Multiple Dose (M97-743)	M97743	Sep 29, 1997	Jan 12, 1998	92	1 Netherla					
Ph I Effect of Food (M97-787)	M97787	Jun 22, 1998	Jul 23, 1998	12	1 U.S.					
Ph I Bio (PIB vs. SEC) (M97-706)		Jun 22, 1998	Aug 22, 1998	24	1 Scotland					
Ph I 14 Day 75mcg BID (M98-907)	M98907	Aug 25, 1998	Sep 24, 1998	12	1					
Ph I Pain Model (M98-899)	M98899	Sep 22, 1998	Nov 21, 1998	12	1 Scotland					
Ph I Bio M98-984 (HGC vs SEC)		Mar 22, 1999	May 21, 1999	24	1 U.S.					
Ph I Bio M99-043 (75ug HGC)	M99043	Jun 30, 1999	Aug 31, 1999	24	1					
Ph I Rising Multi HCG BID Doses		Jul 12, 1999	Sep 10, 1999	50	1 USA					
Human Metabolism (M98-986)	M98971	Jan 1, 2000	Apr 30, 2000	6	1 U.S.					
Ph I Pilot Bio Study (Ph III vs Comm		Jan 10, 2000	Mar 10, 2000	24	0 U.S.					
Ph I Interaction # 1		Jan 10, 2000	Mar 10, 2000	32	1 U.S.					
Ph I Cardiovascular Safety		Feb 1, 2000	May 1, 2000	32	1					
Ph I Single Dose PK in Japanese		Feb 1, 2000	Apr 1, 2000	60	3 Japan					
Ph I PK in Elderly Subjects	M98986	Feb 15, 2000	Apr 29, 2000	48	1 U.S.					
Ph I PK Renal Impaired		Feb 15, 2000	May 15, 2000	32	1 U.S.					
Ph I PK in Smokers		Apr 1, 2000	Jun 30, 2000	48	1 U.S.					
Ph I PK Hepatic Impaired		Apr 1, 2000	Jun 30, 2000	32	1 U.S.					
Ph I Interaction # 2		Apr 1, 2000	May 31, 2000	32	1 U.S.					

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ABBT 0019058

Project Assumption Report

Report As Of: Jun 17, 199

Project Name	Project Number					
ABT-594	G0 143010					
Ph I Interaction # 3	May 1, 2000	Jun 30, 2000	32	1 U.S.		
Ph I Multi Dose PK in Japanese	Jun 1, 2000	Aug 30, 2000	60	2		
Ph I Interaction # 4	Jun 1, 2000	Jul 31, 2000	32	1 U.S.		
Ph I Interaction # 5	Jul 1, 2000	Aug 30, 2000	32	1		
Ph I Effect of Food in Japanese	Aug 1, 2000	Sep 15, 2000	24	1 U.S.		
Ph I Interaction # 6	Aug 1, 2000	Sep 30, 2000	32	1		
Ph I Bio (Ph III Form vs Commercial	Oct 1, 2000	Nov 29, 2000	32	1 U.S.		

Active

Phase : 2

Activity	Protocol	Activity Start	Activity End	No. Patients	No. Sites	Manpower PMP	Manpower TMP	Direct Dollars	Grant Dollars	Comments
Ph II Molar Extraction (M97-772)	M97772	Jun 25, 1998	Oct 23, 1998	290	1 U.S.					
Ph II Molar Extraction (M98-897)	M98897	Aug 10, 1998	Sep 24, 1998	45	1					
Ph II Osteoarthritis (M98-826)	M98826	Oct 26, 1998	Aug 22, 1999	250	20 U.S.					
Ph II Neuropathic Pain (M98-833)	M98833	Oct 28, 1998	Aug 24, 1999	150	10 U.S.					
Ph II Cancer Pain		May 1, 2000	Feb 1, 2001	250	20 U.S.					
Ph II Cancer Pain		May 7, 2000	Feb 7, 2001	250	20 U.S.					

Active

Phase : 3

Activity	Protocol	Activity Start	Activity End	No. Patients	No. Sites	Manpower PMP	Manpower TMP	Direct Dollars	Grant Dollars	Comments
Ph III Osteoarthritis (Pivotal I)		Dec 1, 1999	Nov 30, 2000	600	30 U.S.					
Ph III Osteoarthritis (Pivotal II)		Dec 2, 1999	Dec 1, 2000	600	30 U.S.					
Ph III Osteoarthritis (Pivotal III)		Dec 3, 1999	Nov 27, 2000	600	30 U.S.					
Ph III Osteoarthritis Europe		Dec 5, 1999	Jan 8, 2001	600	40 Europe					
Ph III Long Term Safety Europe		Dec 15, 1999	Jul 1, 2003	300	60 Europe					
Ph III Long Term Safety		Dec 15, 1999	Jul 1, 2003	600	150 U.S.					
Ph III Neuropathic Pain (Pivotal I)		Mar 1, 2000	Mar 29, 2001	600	30 U.S.					
Ph III Neuropathic Pain (Pivotal II)		Mar 8, 2000	Feb 9, 2001	600	30 U.S.					
Ph III Neuropathic Pain (Pivotal III)		Mar 15, 2000	Feb 15, 2001	600	30 U.S.					

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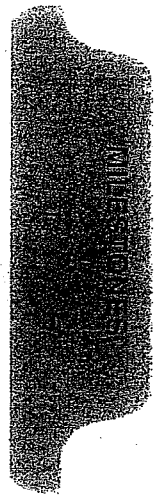
Project Assumption Report

Project Name	Project Number	Report As Of: Jun 17, 199				
ABT-594	G0 143010					
Ph III Neuropathic Pain Europe	Mar 21, 2000	Jan 26, 2001	600	40 Europe		
Ph III Osteoarthritis (Bridging) Japan	Oct 1, 2000	Sep 6, 2001	300	15 Japan		
Ph III Neuropathic (Bridging) Japan	Nov 1, 2000	Sep 27, 2001	300	15 Japan		
Ph IIIB Pricing Study U.S.	Feb 1, 2001	Oct 29, 2001	500	25 U.S.		
Ph IIIB Pricing Study Australia	Mar 1, 2001	Nov 26, 2001	500	25 Australi		
Ph IIIB Pricing Study Canada	Mar 1, 2001	Nov 26, 2001	500	25 Canada		
Ph IIIB Pricing Study Europe	Apr 1, 2001	Dec 27, 2001	500	25 Europe		

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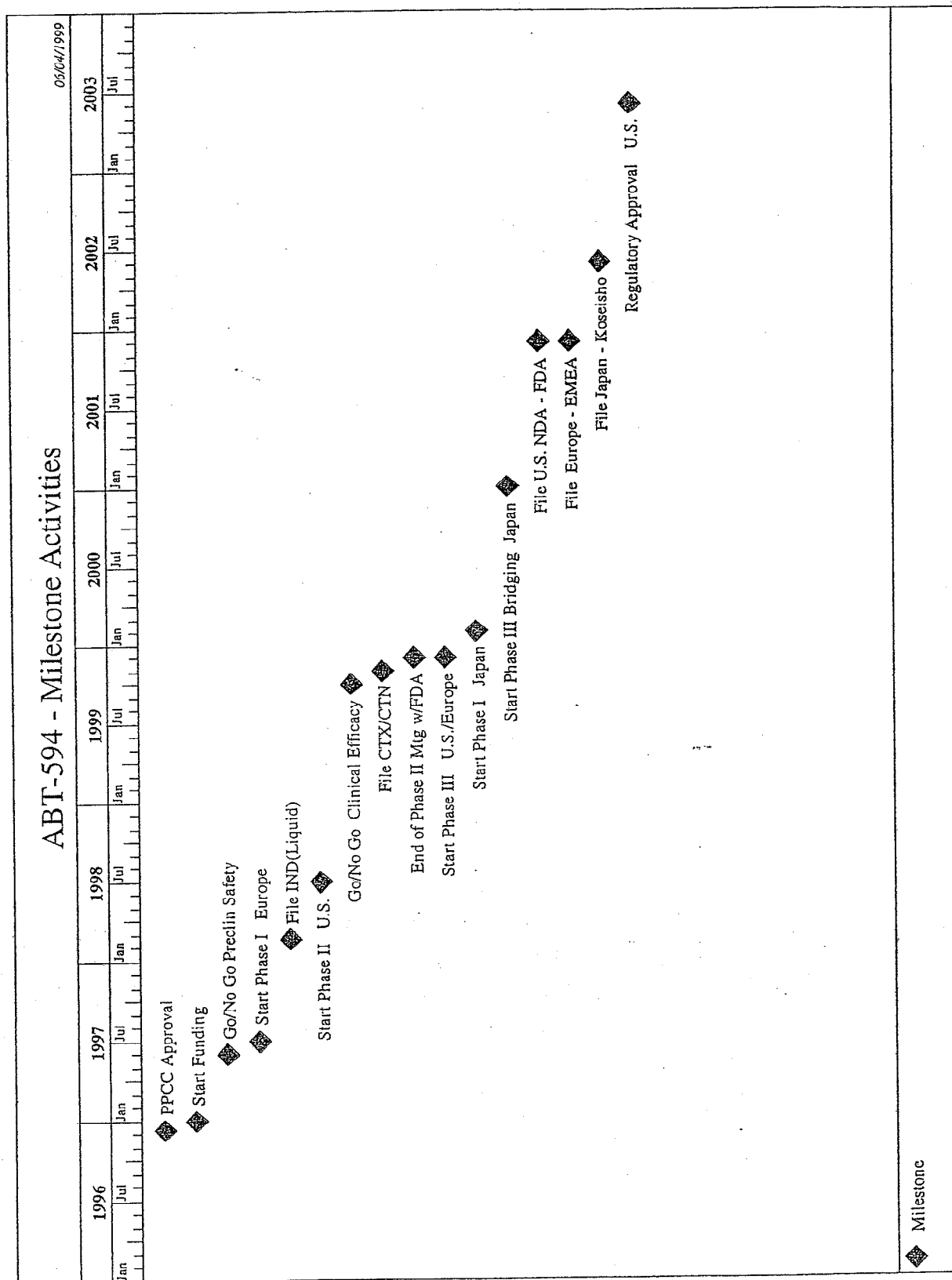
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ABBT 0019060



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ABBT 0019061



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ABBT 0019062

Activity Listing

06/17/99

Sponsor Milestone		Project ABT-594		Indication Pain (General)			
Versio	Plan	Project N	G0 143010	Formulation	Oral Solid		
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
PPCC Approval		NKMSA101	12/10/1996	12/10/1996	12/10/1996	12/10/1996	C
Start Funding		NKMSB102	01/01/1997	01/01/1997	01/01/1997	01/01/1997	C
Go/No Go Preclin Safety		NKMSC103	06/01/1997	06/01/1997	06/01/1997	06/01/1997	C
Start Phase I Europe		NKMSP301	07/01/1997	07/01/1997	07/01/1997	07/01/1997	C
File IND(Liquid)		NKMSD104	02/19/1998	02/19/1998	02/19/1998	02/19/1998	C
Start Phase II U.S.		NKMSD001	07/01/1998	07/01/1998	07/01/1998	07/01/1998	C
Go/No Go Clinical Efficacy		NKMSD002	09/30/1999	09/30/1999	09/30/1999	09/30/1999	A
File CTX/CTN		NKMSD021	10/31/1999	10/31/1999	10/31/1999	10/31/1999	A
End of Phase II Mtg w/FDA		NKMSD020	11/30/1999	11/30/1999	11/30/1999	11/30/1999	A
Start Phase III U.S./Europe		NKMSD004	12/01/1999	02/28/2000	02/28/2000	02/28/2000	A
Start Phase I Japan		NKMSD016	02/01/2000	02/01/2000	02/01/2000	02/01/2000	A
Start Phase III Bridging Japan		NKMSD017	01/01/2001	01/01/2001	01/01/2001	01/01/2001	A
File Europe - EMEA		NKMSD006	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A
File U.S. NDA - FDA		NKMSL112	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A
File Japan - Koseisho		NKMSD019	06/01/2002	06/01/2002	06/01/2002	06/01/2002	A
Regulatory Approval U.S.		NKMSD007	06/01/2003	06/01/2003	06/01/2003	06/01/2003	A

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ABBT 0019063

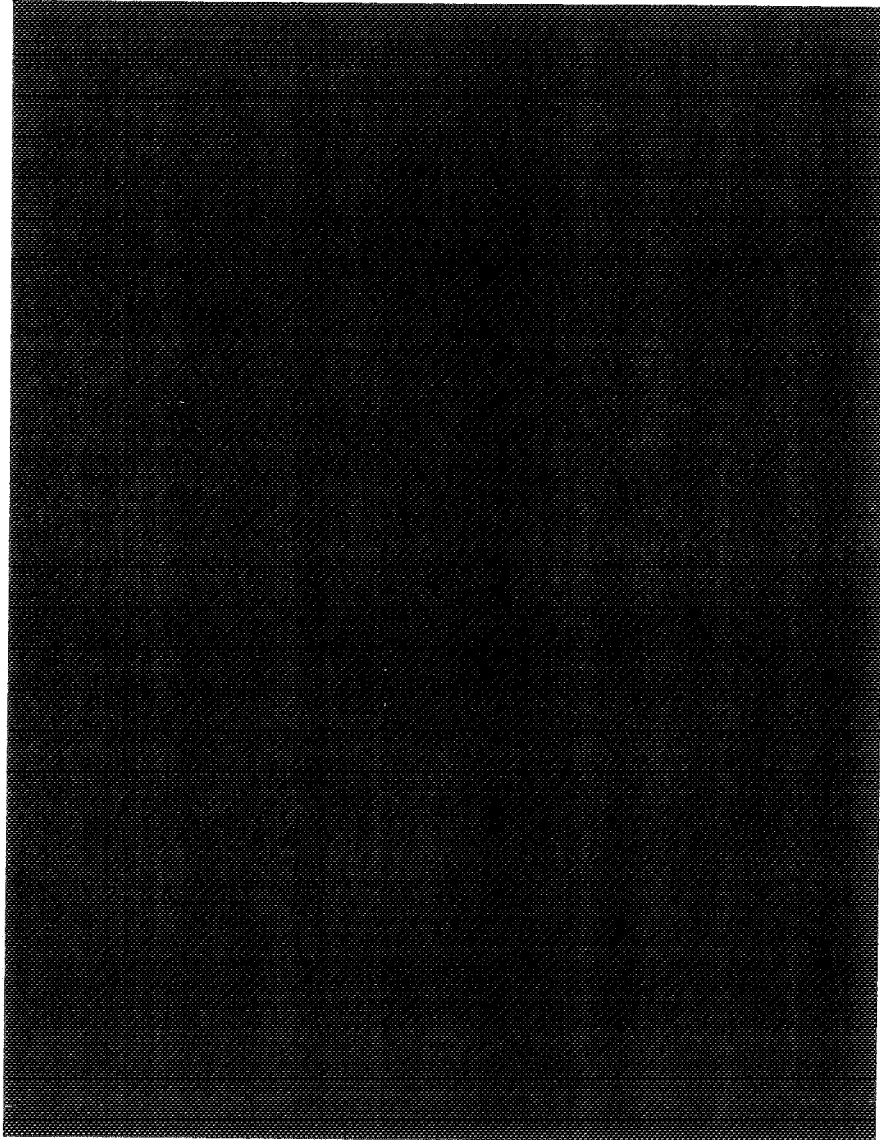
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D's Exhibit GK

ABT-594 Annual Report.
IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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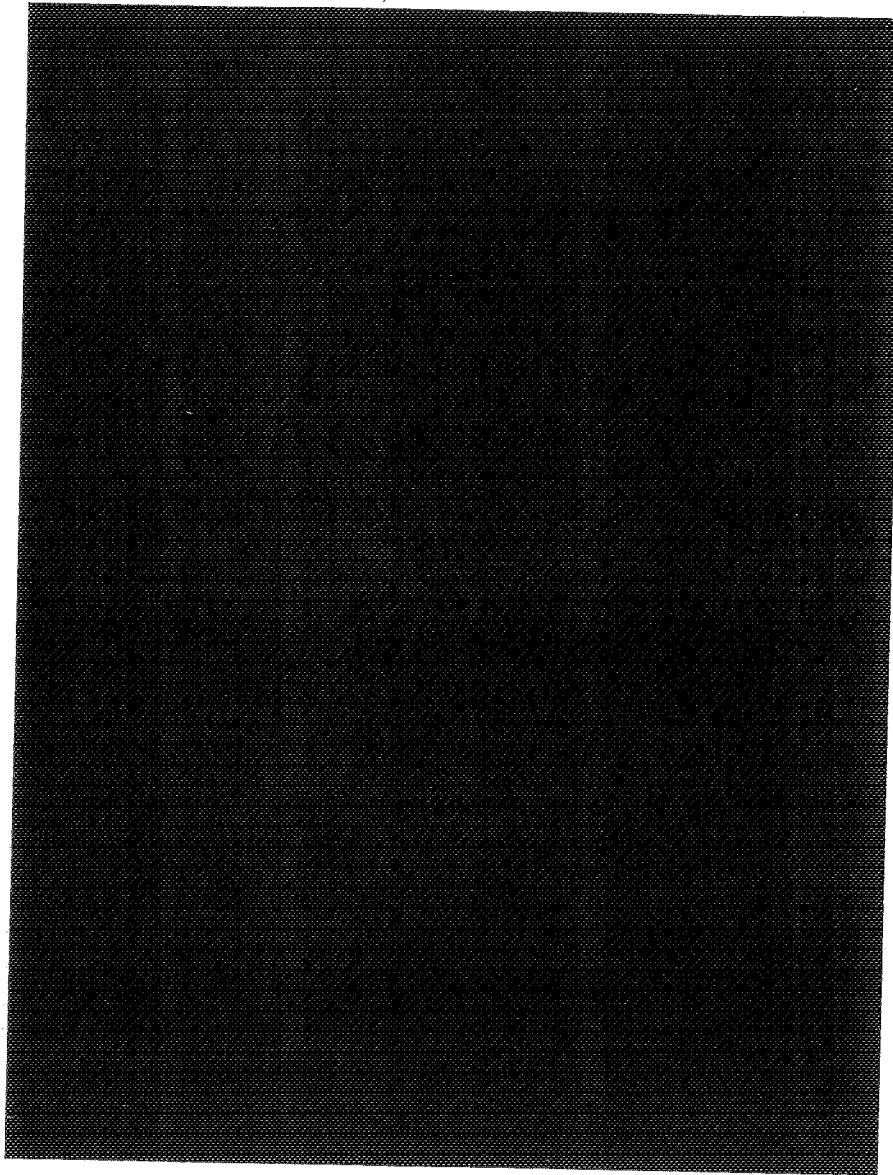
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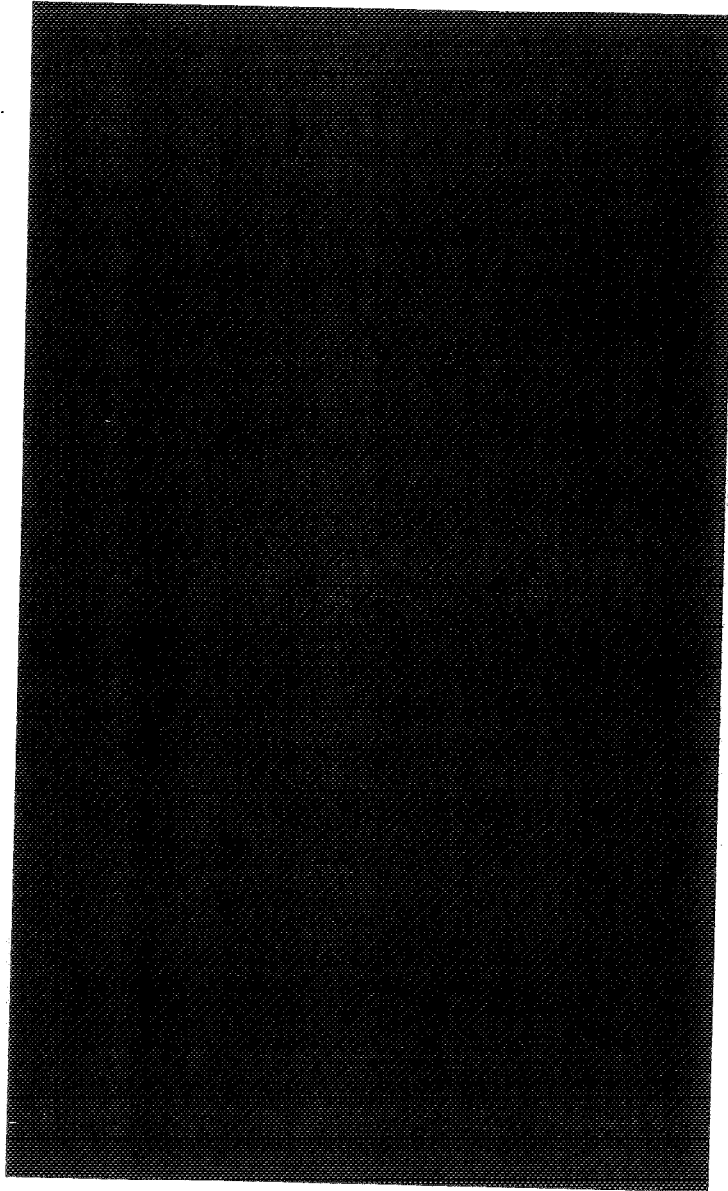
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Part 3

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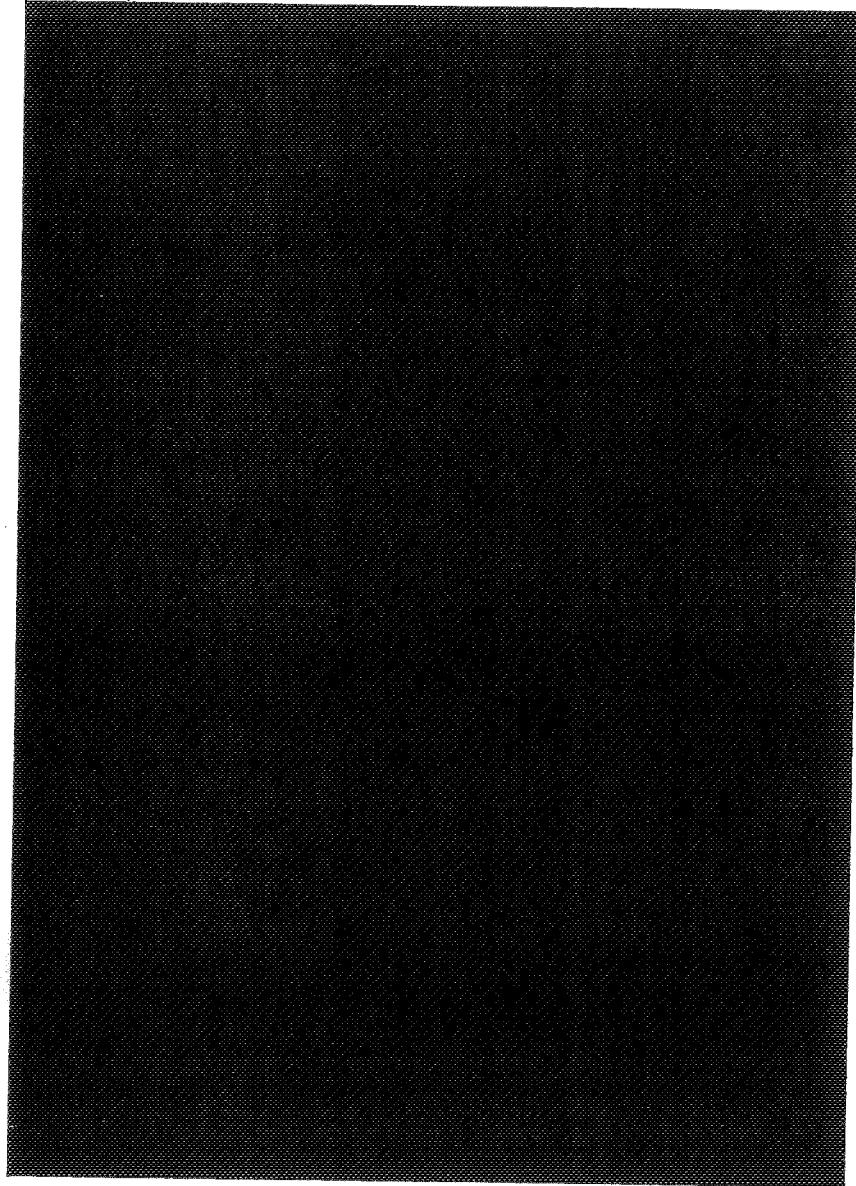
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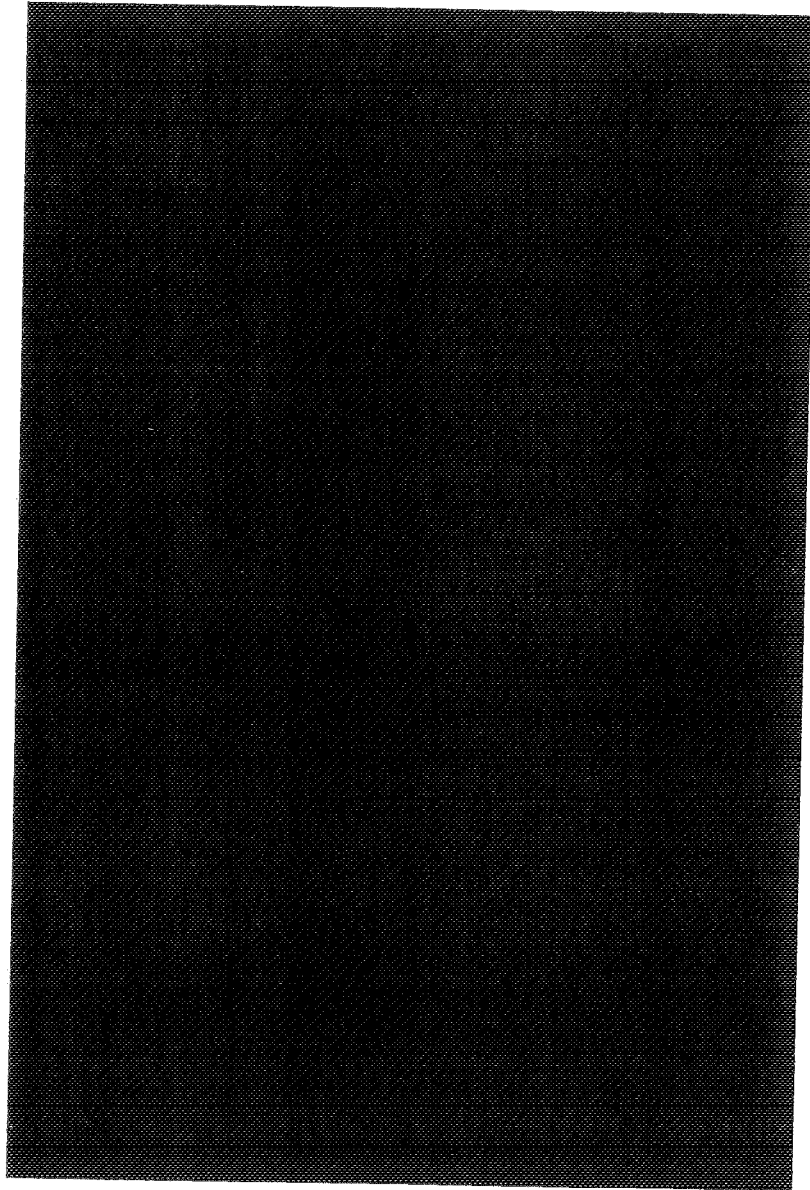
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Part 5

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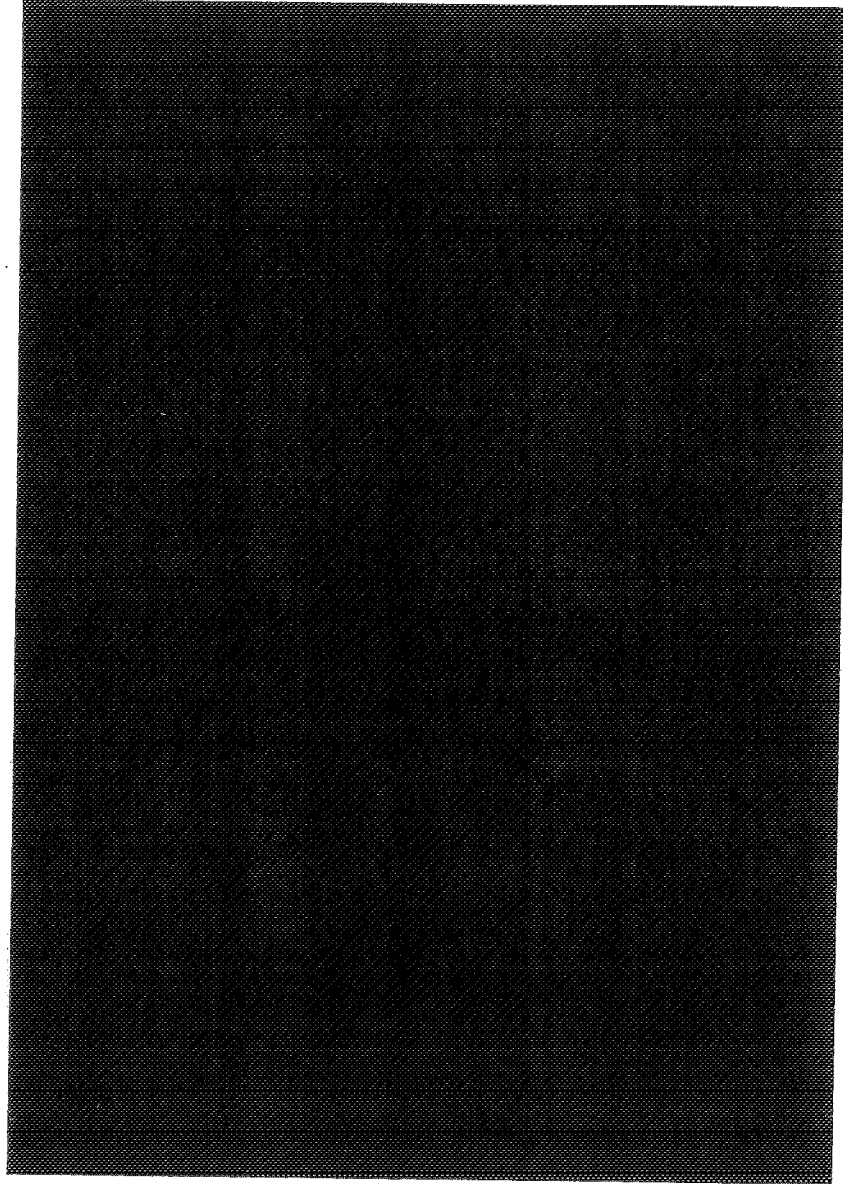
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Part 6

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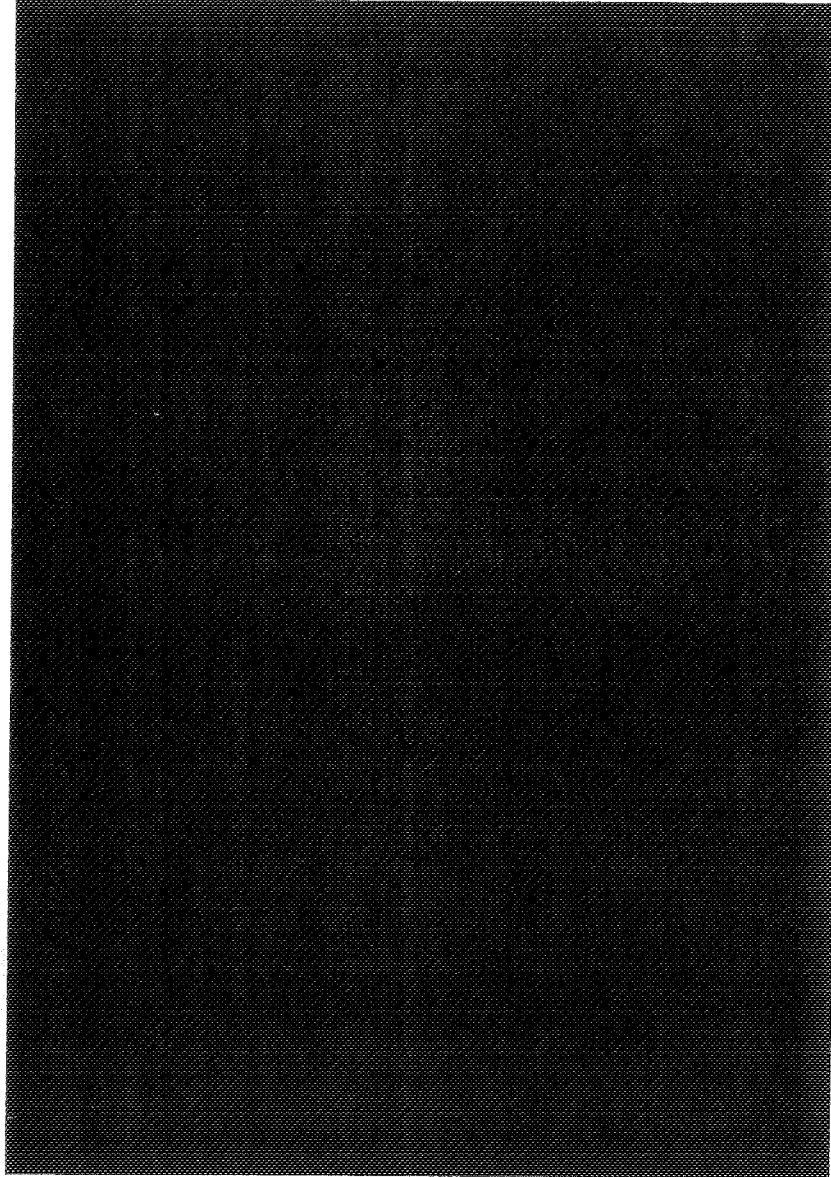
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IND No. 55,293, IND No. 56,980
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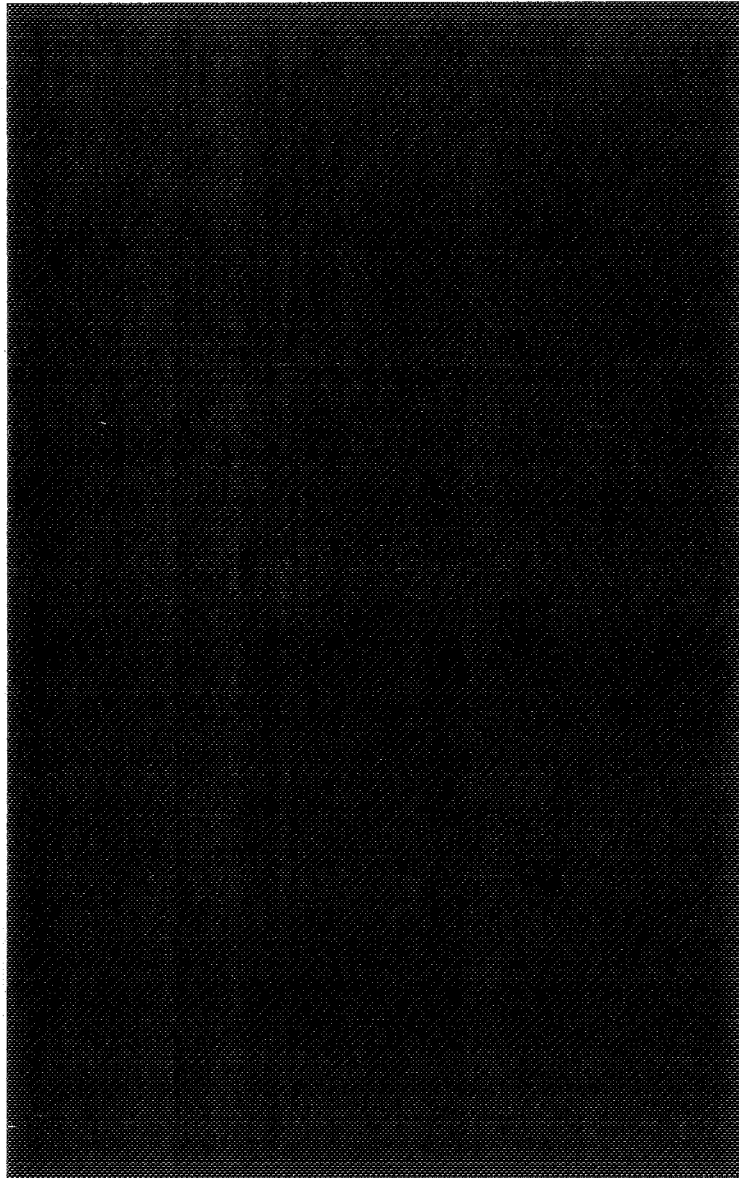
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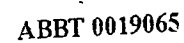
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Part 3



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Activity Listing

06/17/99

Sponsor Pharmacology		Project ABT-594			Indicatio Pain (General)		
Versio	Plan	Project N	G0 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Respiration - Pilot		NKALD001	01/01/1997	04/01/1997	05/01/1997	07/01/1997	C
Drug Discrimination		NKALLB01	01/01/1997	05/21/1997	06/21/1997	07/21/1997	C
Abuse Potential - Self Administration		NKALLB02	01/01/1997	08/01/1997	09/01/1997	10/01/1997	C
Special Pharmacology Studies 1997		NKALLB03	01/01/1997	12/27/1997	12/27/1997	12/27/1997	C
Advanced Renal Profile (GFR)		NKALD004	05/01/1997	07/01/1997	08/01/1997	10/01/1997	C
Respiration - Dose Response		NKALD005	06/23/1997	08/23/1997	08/23/1997	09/22/1997	C
Bronchoconstriction		NKALD006	06/23/1997	08/23/1997	09/01/1997	10/01/1997	C
Cardiovascular/Renal Profile		NKALD002	10/01/1997	10/01/1997	10/01/1997	10/01/1997	C
Special Pharmacology Studies 1998		NKALD008	01/01/1998	12/27/1998	12/27/1998	12/27/1998	C
Special Pharmacology Studies 1999		NKALD007	01/01/1999	12/27/1999	12/27/1999	12/27/1999	A
Special Pharmacology Studies 2000		NKALD010	01/01/2000	12/31/2000	12/31/2000	12/31/2000	A

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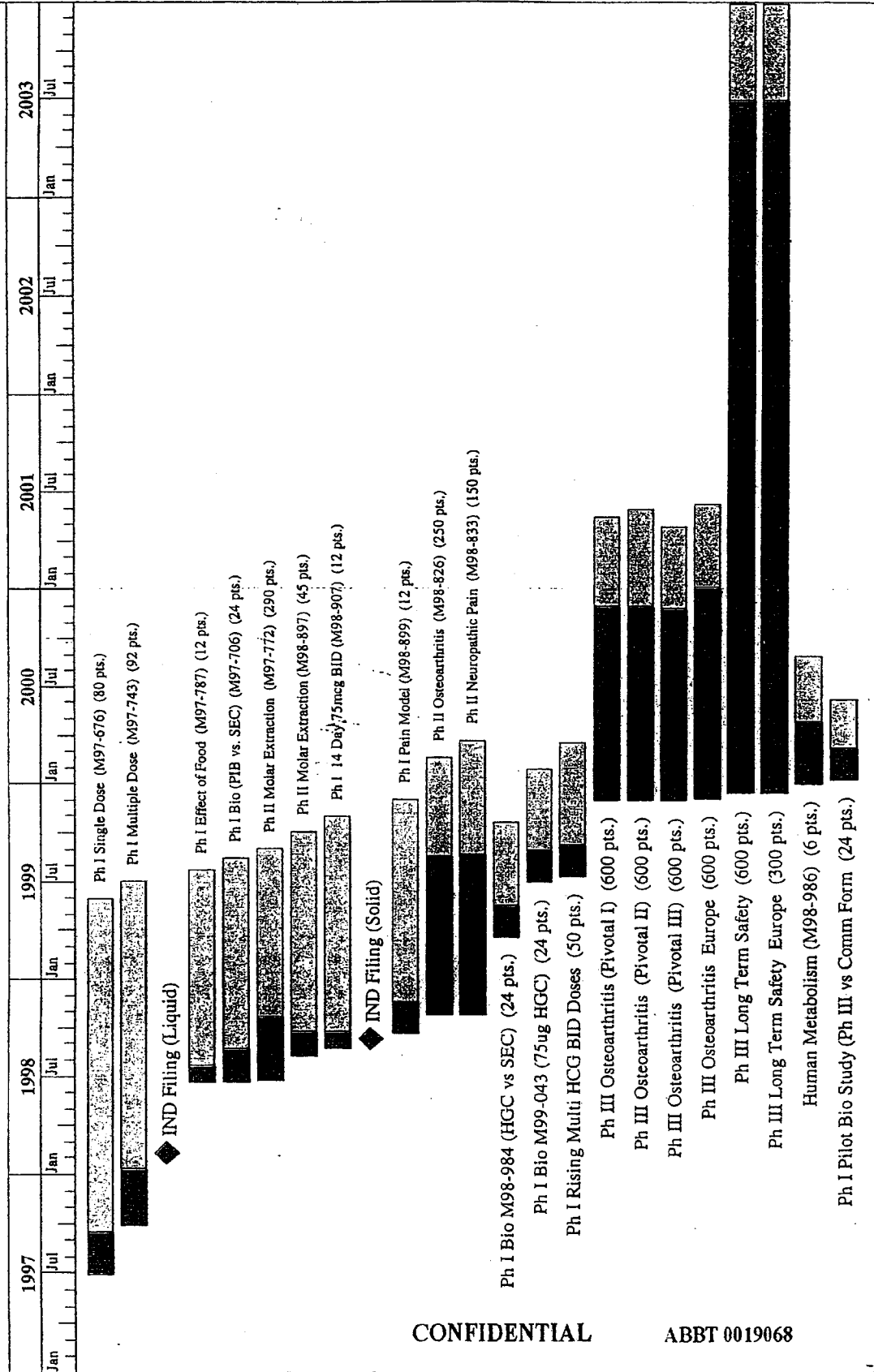


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ABT-594 - Clinical Activities

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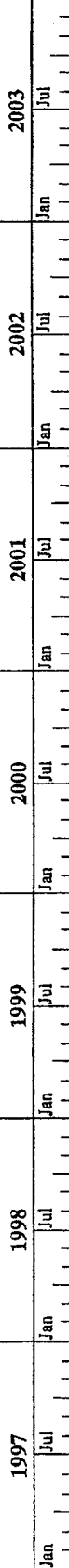
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Clinical

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ABT-594 - Clinical Activities

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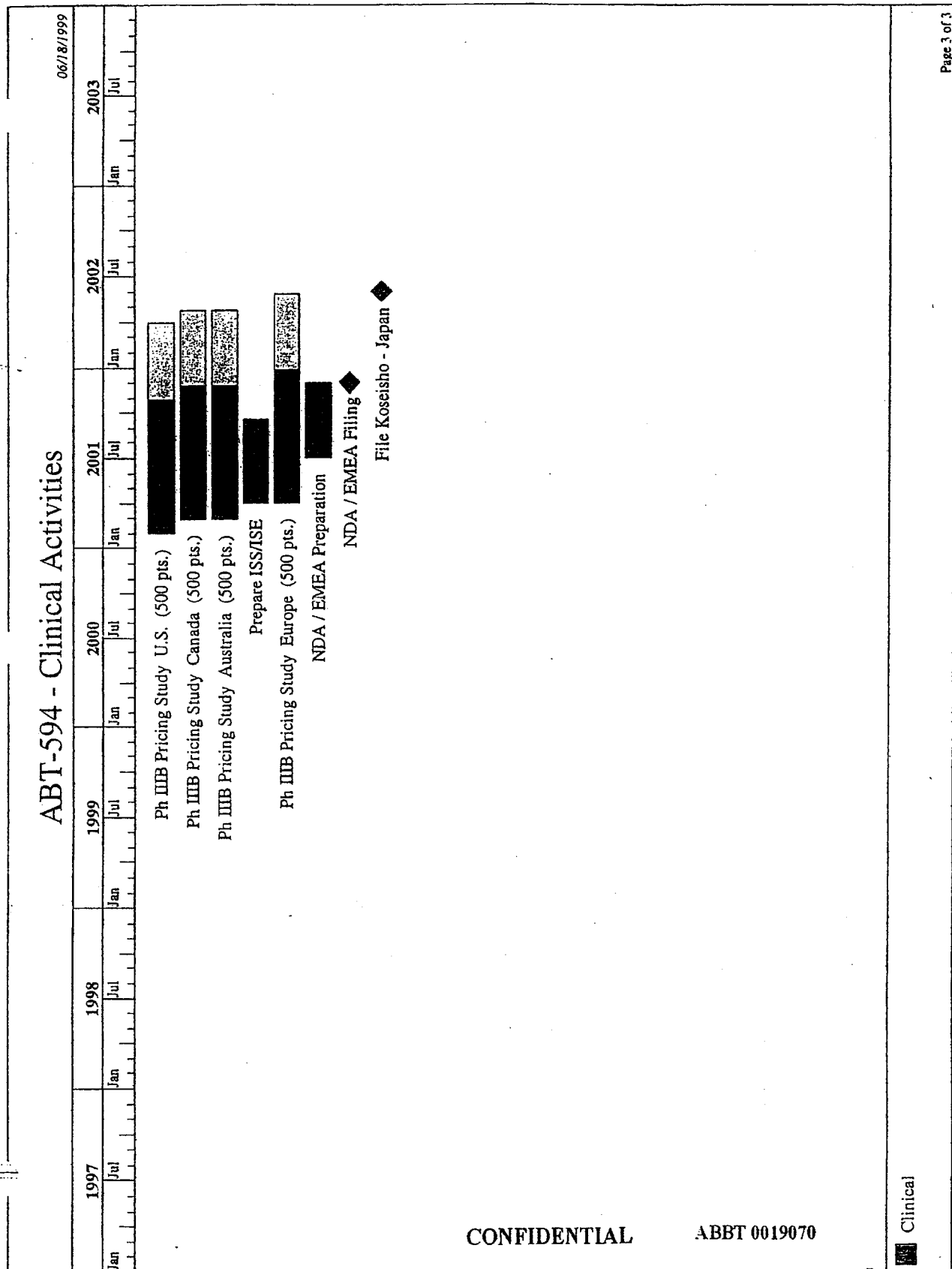


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Clinical

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Activity Listing

06/17/99

Sponsor Clinical	Project	ABT-594	Indication Pain (General)			
Version Plan	Project N	G0 143010	Formulation Oral Solid			
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Ph I Single Dose (M97-676)	NKACP103	07/01/1997	09/15/1997	02/08/1998	05/29/1999	A
Ph I Multiple Dose (M97-743)	NKACP129	09/29/1997	01/12/1998	08/07/1998	07/03/1999	A
IND Filing (Liquid)	NKACPY09	02/09/1998	02/09/1998	02/09/1998	02/09/1998	C
Ph I Effect of Food (M97-787)	NKACP104	06/22/1998	07/23/1998	08/22/1998	07/23/1999	A
Ph I Bio (PIB vs. SEC) (M97-706)	NKACP105	06/22/1998	08/22/1998	09/21/1998	08/12/1999	A
Ph II Molar Extraction (M97-772)	NKACP216	06/25/1998	10/23/1998	11/22/1998	09/01/1999	A
Ph II Molar Extraction (M98-897)	NKACD076	08/10/1998	09/24/1998	10/24/1998	10/01/1999	A
Ph I 14 Day 75mcg BID (M98-907)	NKACD077	08/25/1998	09/24/1998	10/24/1998	11/01/1999	A
IND Filing (Solid)	NKACD068	09/10/1998	09/10/1998	09/10/1998	09/10/1998	C
Ph I Pain Model (M98-899)	NKACD074	09/22/1998	11/21/1998	12/21/1998	12/01/1999	A
Ph II Osteoarthritis (M98-826)	NKACP202	10/26/1998	08/22/1999	09/21/1999	02/18/2000	A
Ph II Neuropathic Pain (M98-833)	NKACP204	10/28/1998	08/24/1999	09/23/1999	03/22/2000	A
Ph I Bio M98-984 (HGC vs SEC)	NKACD062	03/22/1999	05/21/1999	06/20/1999	10/18/1999	A
Ph I Bio M99-043 (75ug HGC)	NKACD082	06/30/1999	08/31/1999	09/30/1999	01/28/2000	A
Ph I Rising Multi HCG BID Doses	NKACP128	07/12/1999	09/10/1999	10/10/1999	03/15/2000	A
Ph III Osteoarthritis (Pivotal I)	NKACP302	12/01/1999	11/30/2000	01/14/2001	05/14/2001	A
Ph III Osteoarthritis (Pivotal II)	NKACD053	12/02/1999	12/01/2000	01/30/2001	05/30/2001	A
Ph III Osteoarthritis (Pivotal III)	NKACD070	12/03/1999	11/27/2000	12/27/2000	04/26/2001	A
Ph III Osteoarthritis Europe	NKACP323	12/05/1999	01/08/2001	02/07/2001	06/07/2001	A
Ph III Long Term Safety Europe	NKACD055	12/15/1999	07/01/2003	08/30/2003	12/28/2003	A
Ph III Long Term Safety	NKACP322	12/15/1999	07/01/2003	08/31/2003	12/29/2003	A
Human Metabolism (M98-986)	NKACP126	01/01/2000	04/30/2000	05/30/2000	08/28/2000	A
Ph I Pilot Bio Study (Ph III vs Comm Form)	NKACD089	01/10/2000	03/10/2000	04/09/2000	06/08/2000	A
Ph I Interaction # 1	NKACD021	01/10/2000	03/10/2000	04/09/2000	08/07/2000	A
Ph I Single Dose PK in Japanese	NKACD065	02/01/2000	04/01/2000	05/01/2000	08/29/2000	A
Ph I Cardiovascular Safety	NKACD078	02/01/2000	05/01/2000	05/31/2000	09/28/2000	A
Ph I PK in Elderly Subjects	NKACD064	02/15/2000	04/29/2000	05/29/2000	09/26/2000	A
Ph I PK Renal Impaired	NKACP109	02/15/2000	05/15/2000	06/14/2000	10/12/2000	A
Ph III Neuropathic Pain (Pivotal I)	NKACD052	03/01/2000	03/29/2001	04/28/2001	08/26/2001	A
Ph III Neuropathic Pain (Pivotal II)	NKACD018	03/08/2000	02/09/2001	03/11/2001	06/09/2001	A
Ph III Neuropathic Pain (Pivotal III)	NKACP301	03/15/2000	02/15/2001	04/16/2001	07/15/2001	A
Ph III Neuropathic Pain Europe	NKACD019	03/21/2000	01/26/2001	03/27/2001	06/25/2001	A
Ph I Interaction # 2	NKACD022	04/01/2000	05/31/2000	06/30/2000	09/28/2000	A
Ph I PK in Smokers	NKACD063	04/01/2000	06/30/2000	07/30/2000	11/27/2000	A

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Activity Listing

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<i>Sponsor</i> Clinical	<i>Project</i> ABT-594	<i>Indication</i> Pain (General)				
<i>Version</i> Plan	<i>Project N</i> GO 143010	<i>Formulation</i> Oral Solid				
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Ph I PK Hepatic Impaired	NKACP110	04/01/2000	06/30/2000	07/31/2000	10/29/2000	A
Ph I Interaction # 3	NKACP112	05/01/2000	06/30/2000	07/30/2000	10/28/2000	A
Ph II Cancer Pain	NKACD083	05/01/2000	02/01/2001	04/01/2001	07/01/2001	A
Ph II Cancer Pain	NKACD084	05/07/2000	02/07/2001	03/15/2001	06/15/2001	A
Ph I Interaction # 4	NKACP113	06/01/2000	07/31/2000	08/30/2000	11/28/2000	A
Ph I Multi Dose PK in Japanese	NKACD080	06/01/2000	08/30/2000	09/29/2000	01/27/2001	A
Ph I Interaction # 5	NKACD025	07/01/2000	08/30/2000	09/29/2000	12/28/2000	A
Ph I Effect of Food in Japanese	NKACD066	08/01/2000	09/15/2000	10/15/2000	01/13/2001	A
Ph I Interaction # 6	NKACD026	08/01/2000	09/30/2000	10/30/2000	01/28/2001	A
Ph I Bio (Ph III Form vs Commercial Form)	NKACP130	10/01/2000	11/29/2000	12/30/2000	12/30/2000	A
Ph III Osteoarthritis (Bridging) Japan	NKACD010	10/01/2000	09/06/2001	11/05/2001	03/05/2002	A
Ph III Neuropathic (Bridging) Japan	NKACD081	11/01/2000	09/27/2001	10/27/2001	02/24/2002	A
Ph IIIB Pricing Study U.S.	NKACD058	02/01/2001	10/29/2001	11/28/2001	03/28/2002	A
Ph IIIB Pricing Study Australia	NKACD061	03/01/2001	11/26/2001	12/26/2001	04/25/2002	A
Ph IIIB Pricing Study Canada	NKACD060	03/01/2001	11/26/2001	12/26/2001	04/25/2002	A
Prepare ISS/ISE	NKACPY03	04/01/2001	09/15/2001	09/15/2001	09/15/2001	A
Ph IIIB Pricing Study Europe	NKACD059	04/01/2001	12/27/2001	01/26/2002	05/26/2002	A
NDA / EMEA Preparation	NKACPY01	07/01/2001	11/29/2001	11/29/2001	11/29/2001	A
NDA / EMEA Filing	NKACPY08	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A
File Koscisho - Japan	NKACD090	06/01/2002	06/01/2002	06/01/2002	06/01/2002	A

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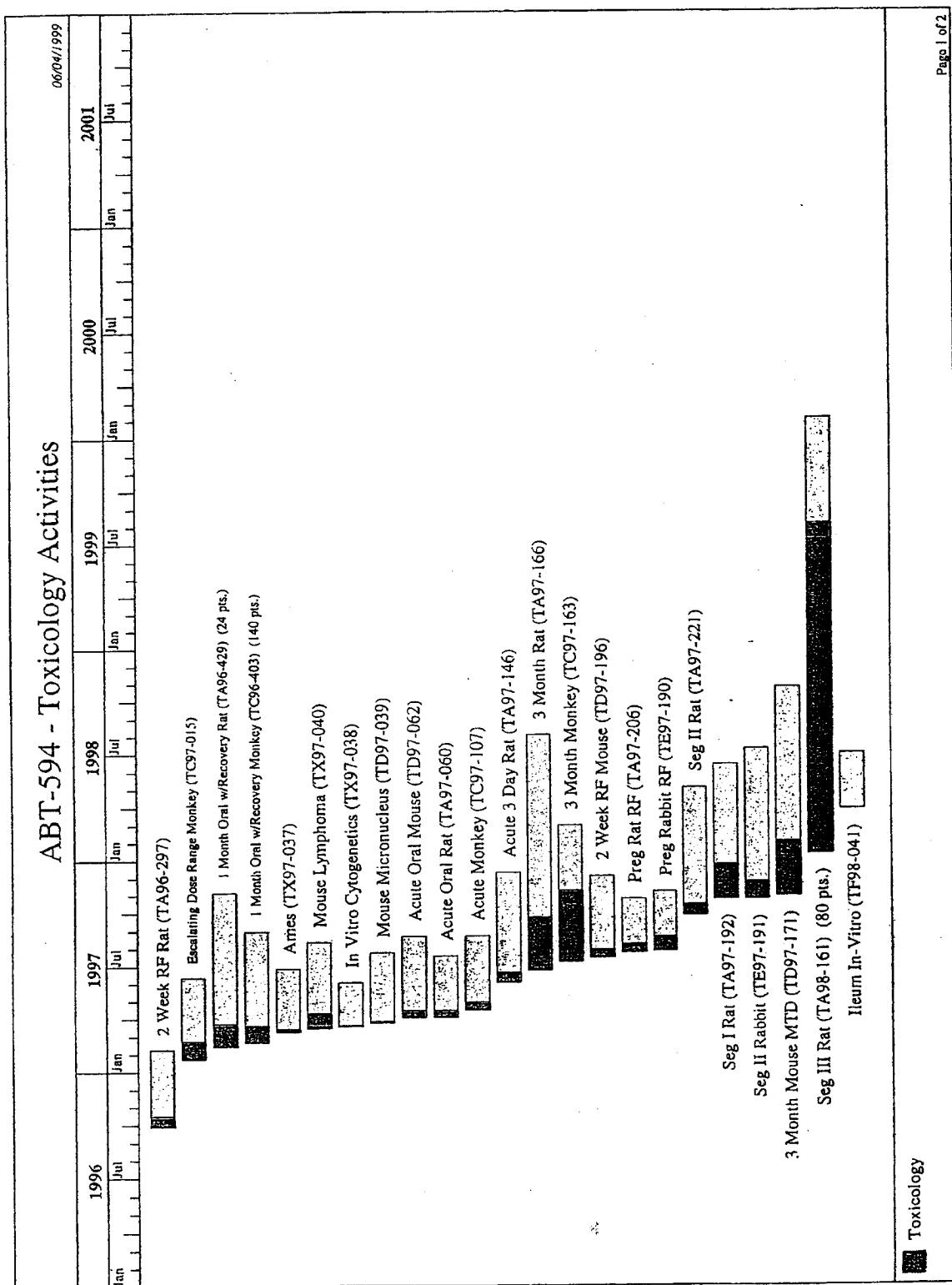
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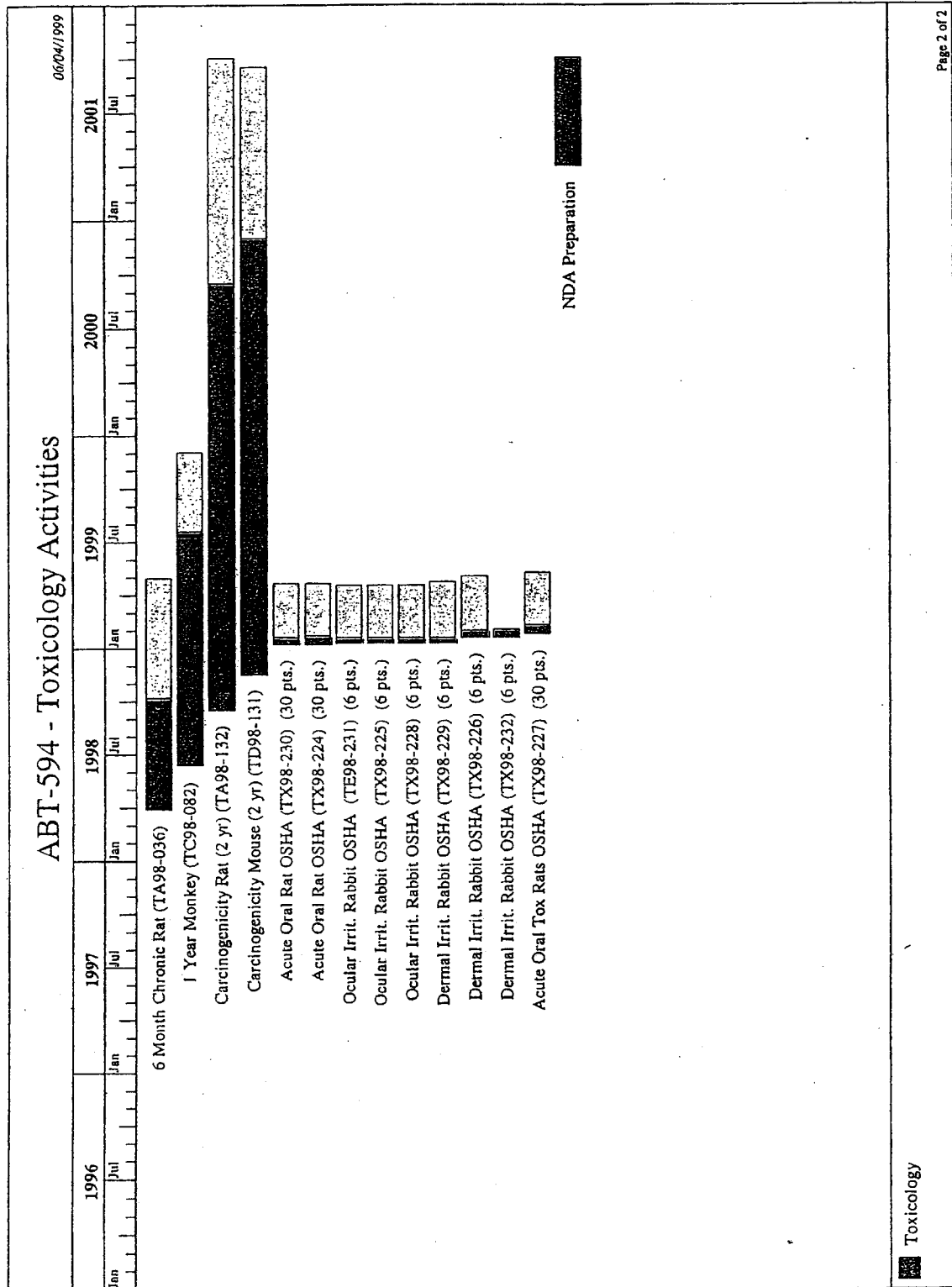
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Activity Listing

06/17/99

Sponsor Toxicology		Project ABT-594		Indicatio Pain (General)			
Version	Plan	Project N	G0 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
2 Week RF Rat (TA96-297)		NKATD013	09/26/1996	10/15/1996	10/15/1996	02/05/1997	C
Escalating Dose Range Monkey (TC97-015)		NKATD014	01/23/1997	02/22/1997	02/22/1997	06/12/1997	C
1 Month Oral w/Recovery Rat (TA96-429)		NKATST01	02/11/1997	03/25/1997	04/25/1997	11/05/1997	C
1 Month Oral w/Recovery Monkey (TC96-403)		NKATST04	02/18/1997	03/21/1997	03/21/1997	08/29/1997	C
Ames (TX97-037)		NKATTM06	03/10/1997	03/14/1997	05/01/1997	06/26/1997	C
Mouse Lymphoma (TX97-040)		NKATMU01	03/15/1997	04/12/1997	04/12/1997	08/11/1997	C
In Vitro Cytogenetics (TX97-038)		NKATTB02	03/17/1997	03/21/1997	06/01/1997	06/01/1997	C
Mouse Micronucleus (TD97-039)		NKATTM07	03/24/1997	03/28/1997	06/05/1997	07/23/1997	C
Acute Oral Rat (TA97-060)		NKATST02	04/01/1997	04/15/1997	04/15/1997	07/17/1997	C
Acute Oral Mouse (TD97-062)		NKATST03	04/01/1997	04/15/1997	04/15/1997	08/21/1997	C
Acute Monkey (TC97-107)		NKATTA01	04/15/1997	04/29/1997	04/29/1997	08/21/1997	C
Acute 3 Day Rat (TA97-146)		NKATD001	06/02/1997	06/19/1997	06/19/1997	12/08/1997	C
3 Month Rat (TA97-166)		NKATTB08	06/24/1997	09/23/1997	12/01/1997	08/03/1998	C
3 Month Monkey (TC97-163)		NKATTB09	07/09/1997	11/06/1997	12/16/1997	02/28/1998	C
2 Week RF Mouse (TD97-196)		NKATTS16	07/15/1997	07/30/1997	07/30/1997	11/30/1997	C
Preg Rat RF (TA97-206)		NKATTT10	07/24/1997	08/07/1997	08/07/1997	10/24/1997	C
Preg Rabbit RF (TE97-190)		NKATTT11	07/28/1997	08/20/1997	08/20/1997	11/05/1997	C
Seg II Rat (TA97-221)		NKATTT12	09/24/1997	10/14/1997	10/14/1997	05/01/1998	C
Seg II Rabbit (TE97-191)		NKATTT13	10/22/1997	11/21/1997	11/21/1997	07/07/1998	C
Seg I Rat (TA97-192)		NKATTT14	10/22/1997	12/22/1997	12/22/1997	06/10/1998	C
3 Month Mouse MTD (TD97-171)		NKATTC19	10/30/1997	01/30/1998	01/30/1998	10/23/1998	C
Seg III Rat (TA98-161)		NKATTT15	01/10/1998	08/04/1999	09/01/1999	01/31/2000	A
Ileum In-Vitro (TF98-041)		NKATXX34	03/24/1998	03/27/1998	03/27/1998	06/29/1998	C
6 Month Chronic Rat (TA98-036)		NKATCR33	03/31/1998	10/07/1998	11/06/1998	04/30/1999	C
1 Year Monkey (TC98-082)		NKATCR39	06/15/1998	07/22/1999	08/06/1999	11/30/1999	A
Carcinogenicity Rat (2 yr) (TA98-132)		NKATD010	09/17/1998	09/15/2000	10/15/2000	09/30/2001	A
Carcinogenicity Mouse (2 yr) (TD98-131)		NKATD011	11/15/1998	12/01/2000	02/01/2001	09/15/2001	A
Acute Oral Rat OSHA (TX98-230)		NKATT004	01/06/1999	01/20/1999	01/20/1999	04/20/1999	C
Acute Oral Rat OSHA (TX98-224)		NKATT007	01/07/1999	01/21/1999	01/21/1999	04/21/1999	C
Ocular Irrit. Rabbit OSHA (TX98-225)		NKATT008	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Ocular Irrit. Rabbit OSHA (TE98-231)		NKATT005	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Dermal Irrit. Rabbit OSHA (TX98-229)		NKATT003	01/11/1999	01/18/1999	01/18/1999	04/22/1999	C
Ocular Irrit. Rabbit OSHA (TX98-228)		NKATT002	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Dermal Irrit. Rabbit OSHA (TX98-226)		NKATT009	01/18/1999	02/01/1999	02/01/1999	05/02/1999	A

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Activity Listing

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<i>Sponsor</i>	Toxicology	<i>Project</i>	ABT-594		<i>Indicatio</i>	Pain (General)	
<i>Version</i>	Plan	<i>Project N</i>	G0 143010		<i>Formulation</i>	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Dermal Irrit. Rabbit OSHA (TX98-232)		NKATT006	01/18/1999	02/01/1999	02/01/1999	02/01/1999	C
Acute Oral Tox Rats OSHA (TX98-227)		NKATT010	01/25/1999	02/08/1999	02/08/1999	05/09/1999	A
NDA Preparation		NKATD012	04/01/2001	10/01/2001	10/01/2001	10/01/2001	A

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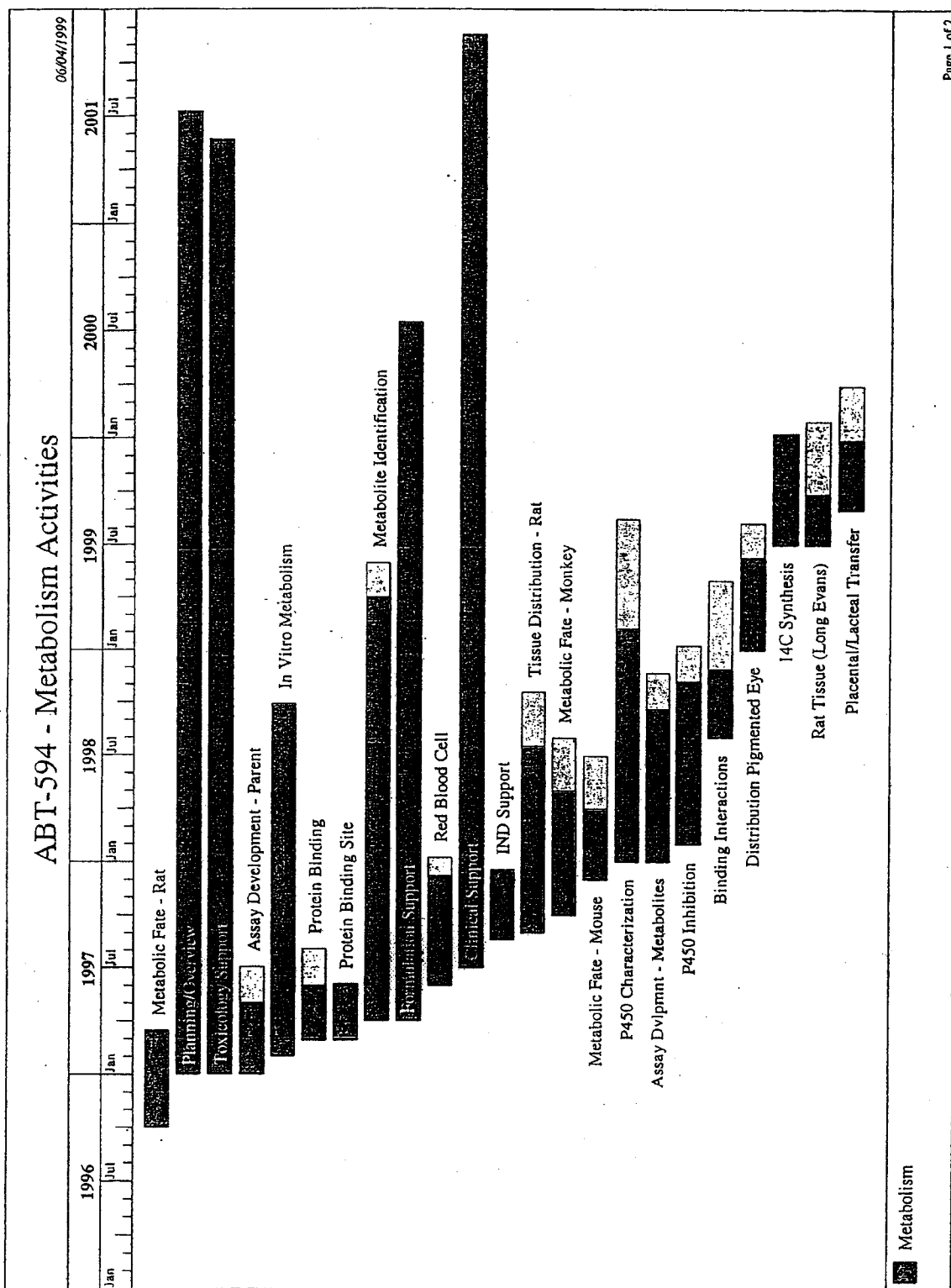
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Activity Listing

06/17/99

<i>Sponsor</i> Metabolism	<i>Project</i> ABT-594	<i>Indication</i> Pain (General)				
<i>Version</i> Plan	<i>Project N</i> G0 143010	<i>Formulation</i> Oral Solid				
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Metabolic Fate - Rat	NKAMMB03	10/01/1996	03/15/1997	03/15/1997	03/15/1997	C
Assay Development - Parent	NKAMMA02	01/01/1997	05/02/1997	07/01/1997	07/01/1997	C
Toxicology Support	NKAMD005	01/01/1997	05/20/2001	05/20/2001	05/20/2001	A
Planning/Overview	NKAMMS01	01/01/1997	07/09/2001	07/09/2001	07/09/2001	A
In Vitro Metabolism	NKAMMB14	02/01/1997	09/24/1998	09/24/1998	09/24/1998	C
Protein Binding Site	NKAMML01	03/01/1997	06/01/1997	06/01/1997	06/01/1997	C
Protein Binding	NKAMMB08	03/01/1997	06/01/1997	08/01/1997	08/01/1997	C
Metabolite Identification	NKAMMB06	04/01/1997	04/01/1999	04/01/1999	05/31/1999	A
Formulation Support	NKAMMS02	04/01/1997	07/14/2000	07/14/2000	07/14/2000	A
Red Blood Cell	NKAMMB01	06/01/1997	12/08/1997	12/08/1997	01/07/1998	C
Clinical Support	NKAMD006	07/01/1997	11/17/2001	11/17/2001	11/17/2001	A
IND Support	NKAMD002	08/19/1997	12/17/1997	12/17/1997	12/17/1997	C
Tissue Distribution - Rat	NKAMMB13	09/01/1997	07/18/1998	07/18/1998	10/16/1998	C
Metabolic Fate - Monkey	NKAMMB04	10/01/1997	05/01/1998	05/01/1998	07/30/1998	C
Metabolic Fate - Mouse	NKAMMB11	12/01/1997	04/01/1998	04/01/1998	06/30/1998	C
Assay Development - Metabolites	NKAMMA03	01/01/1998	09/18/1998	11/19/1998	11/19/1998	C
P450 Characterization	NKAMMB05	01/01/1998	02/05/1999	02/05/1999	08/14/1999	A
P450 Inhibition	NKAMMA01	02/01/1998	11/08/1998	11/08/1998	01/07/1999	C
Binding Interactions	NKAMMB09	08/01/1998	11/29/1998	12/29/1998	04/28/1999	C
Distribution Pigmented Eye	NKAMMB02	01/01/1999	06/10/1999	06/10/1999	08/09/1999	A
Rat Tissue (Long Evans)	NKAMD008	07/01/1999	09/29/1999	10/29/1999	01/27/2000	A
¹⁴ C Synthesis	NKAMMS07	07/01/1999	01/07/2000	01/07/2000	01/07/2000	C
Placental/Lactal Transfer	NKAMD007	09/01/1999	12/30/1999	12/30/1999	03/29/2000	A
Metabolic Fate - Man	NKAMMB07	01/02/2000	05/21/2000	08/21/2000	11/19/2000	A
NDA Support	NKAMD003	01/01/2001	05/01/2001	05/01/2001	05/01/2001	A

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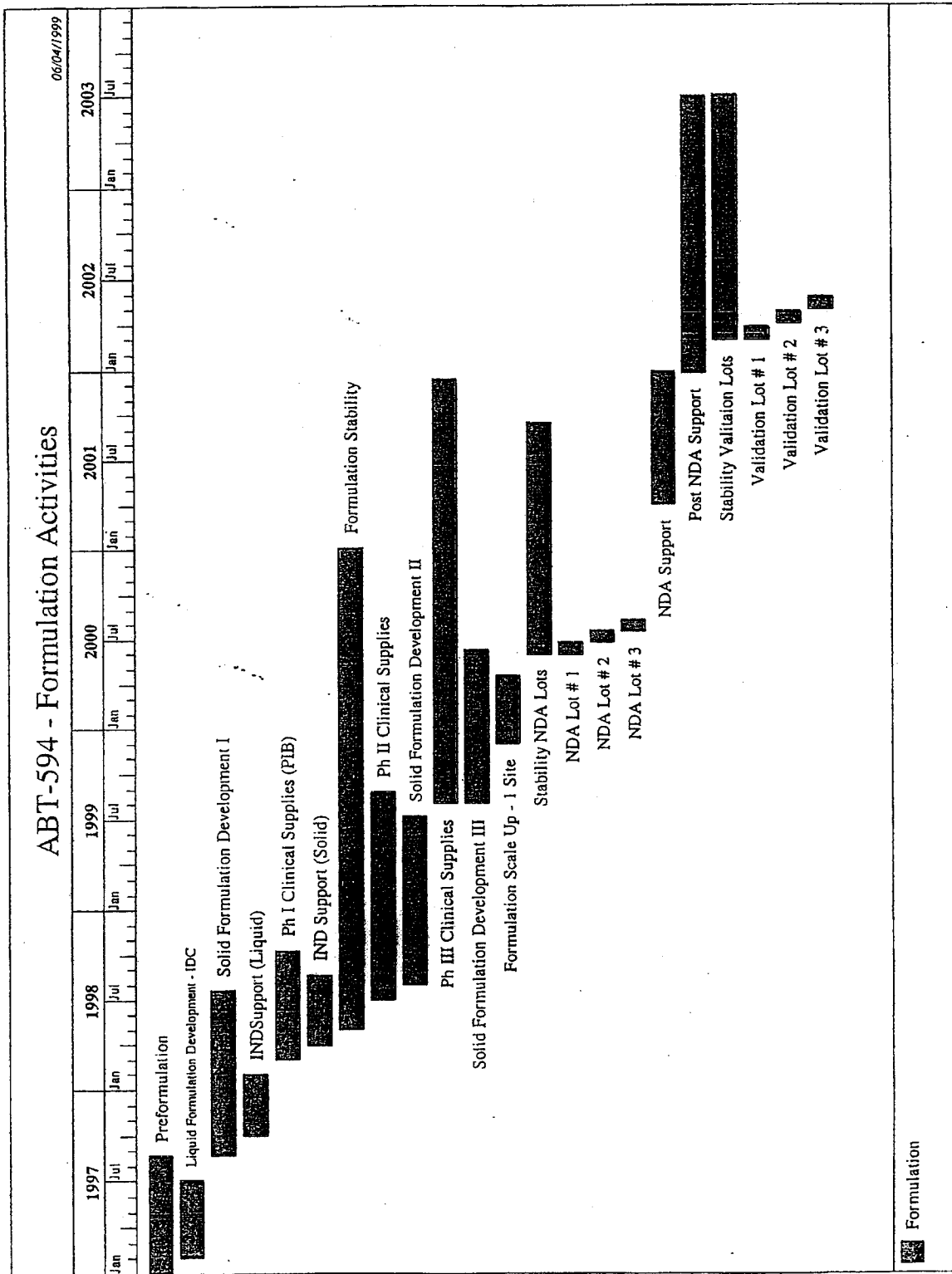
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ABBT 0019083

Activity Listing

06/17/99

Sponsor Formulation		Project ABT-594		Indication Pain (General)			
Version	Plan	Project N	GO 143010		Formulation	Oral Solid	
Description		AN Num	Stry Start	Stry End	DB End	Sum End	Status Code
Preformulation		NKAWWD01	01/01/1997	08/19/1997	08/19/1997	08/19/1997	C
Liquid Formulation Development - IDC		NKAWD004	02/01/1997	07/01/1997	07/01/1997	07/01/1997	C
Solid Formulation Development I		NKAWWF02	08/22/1997	07/18/1998	07/18/1998	07/18/1998	C
INDSupport (Liquid)		NKAWD005	10/01/1997	01/29/1998	01/29/1998	01/29/1998	C
Ph I Clinical Supplies (PIB)		NKAWWG03	03/01/1998	10/07/1998	10/07/1998	10/07/1998	C
IND Support (Solid)		NKAWD009	04/01/1998	08/19/1998	08/19/1998	08/19/1998	C
Formulation Stability		NKAWD008	05/01/1998	01/01/2001	01/01/2001	01/01/2001	A
Ph II Clinical Supplies		NKAWWG05	07/01/1998	08/25/1999	08/25/1999	08/25/1999	A
Solid Formulation Development II		NKAWWF07	08/01/1998	07/07/1999	07/07/1999	07/07/1999	A
Solid Formulation Development III		NKAWWF04	08/01/1999	06/06/2000	06/06/2000	06/06/2000	A
Ph III Clinical Supplies		NKAWWG11	08/01/1999	12/08/2001	12/08/2001	12/08/2001	A
Formulation Scale Up - 1 Site		NKAWD010	12/01/1999	04/14/2000	04/14/2000	04/14/2000	A
Stability NDA Lots		NKAWD014	05/30/2000	09/12/2001	09/12/2001	09/12/2001	A
NDA Lot # 1		NKAWD011	06/01/2000	06/22/2000	06/22/2000	06/22/2000	A
NDA Lot # 2		NKAWD012	06/23/2000	07/14/2000	07/14/2000	07/14/2000	A
NDA Lot # 3		NKAWD013	07/15/2000	08/05/2000	08/05/2000	08/05/2000	A
NDA Support		NKAWD006	04/01/2001	12/22/2001	12/22/2001	12/22/2001	A
Post NDA Support		NKAWWS09	12/22/2001	06/25/2003	06/25/2003	06/25/2003	A
Stability Valitation Lots		NKAWD018	02/28/2002	06/30/2003	06/30/2003	06/30/2003	A
Validation Lot # 1		NKAWD015	03/01/2002	03/22/2002	03/22/2002	03/22/2002	A
Validation Lot # 2		NKAWD016	04/01/2002	04/22/2002	04/22/2002	04/22/2002	A
Validation Lot # 3		NKAWD017	05/01/2002	05/22/2002	05/22/2002	05/22/2002	A

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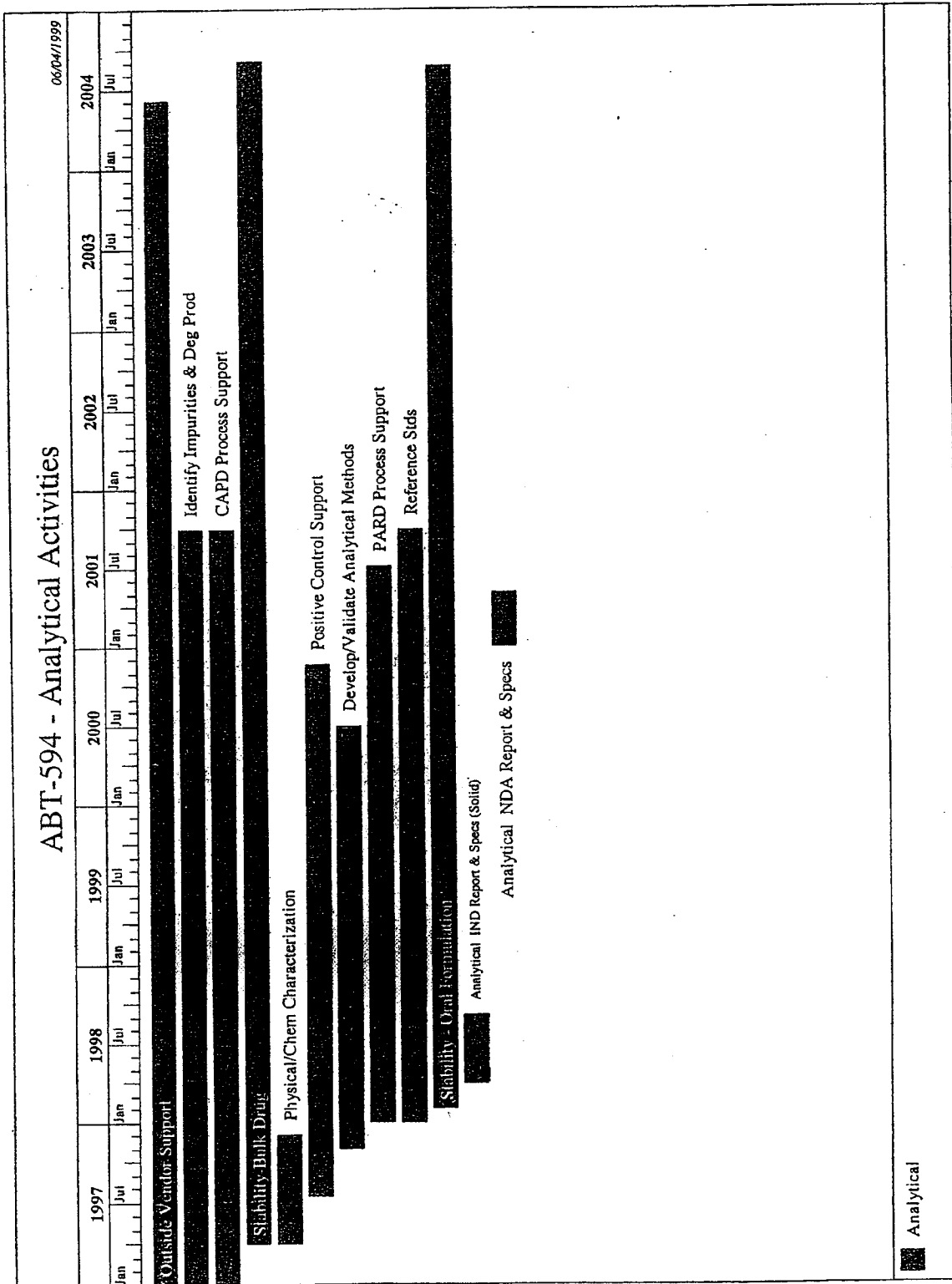
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Activity Listing

06/17/99

Sponsor Analytical		Project ABT-594			Indicatio Pain (General)		
Versio	Plan	Project N	GO 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Identify Impurities & Deg Prod		NKA VWC03	01/01/1997	09/27/2001	09/27/2001	09/27/2001	A
CAPD Process Support		NKA VD005	01/01/1997	09/27/2001	09/27/2001	09/27/2001	A
Outside Vendor Support		NKA VD006	01/01/1997	06/01/2004	06/01/2004	06/01/2004	A
Physical/Chem Characterization		NKA VWC07	04/01/1997	12/01/1997	12/01/1997	12/01/1997	C
Stability-Bulk Drug		NKA VD002	04/01/1997	08/30/2004	08/30/2004	08/30/2004	A
Positive Control Support		NKA VD010	07/15/1997	11/16/2000	11/16/2000	11/16/2000	A
Develop/Validate Analytical Methods		NKA VWC01	11/01/1997	06/28/2000	06/28/2000	06/28/2000	A
PARD Process Support		NKA VD009	01/01/1998	07/04/2001	07/04/2001	07/04/2001	A
Reference Stds		NKA VWC04	01/01/1998	09/27/2001	09/27/2001	09/27/2001	A
Stability - Oral Formulation		NKA VWC02	02/01/1998	08/18/2004	08/18/2004	08/18/2004	A
Analytical IND Report & Specs (Solid)		NKA VWS02	04/01/1998	09/01/1998	09/01/1998	09/01/1998	A
Analytical NDA Report & Specs		NKA VWS05	01/01/2001	05/01/2001	05/01/2001	05/01/2001	A

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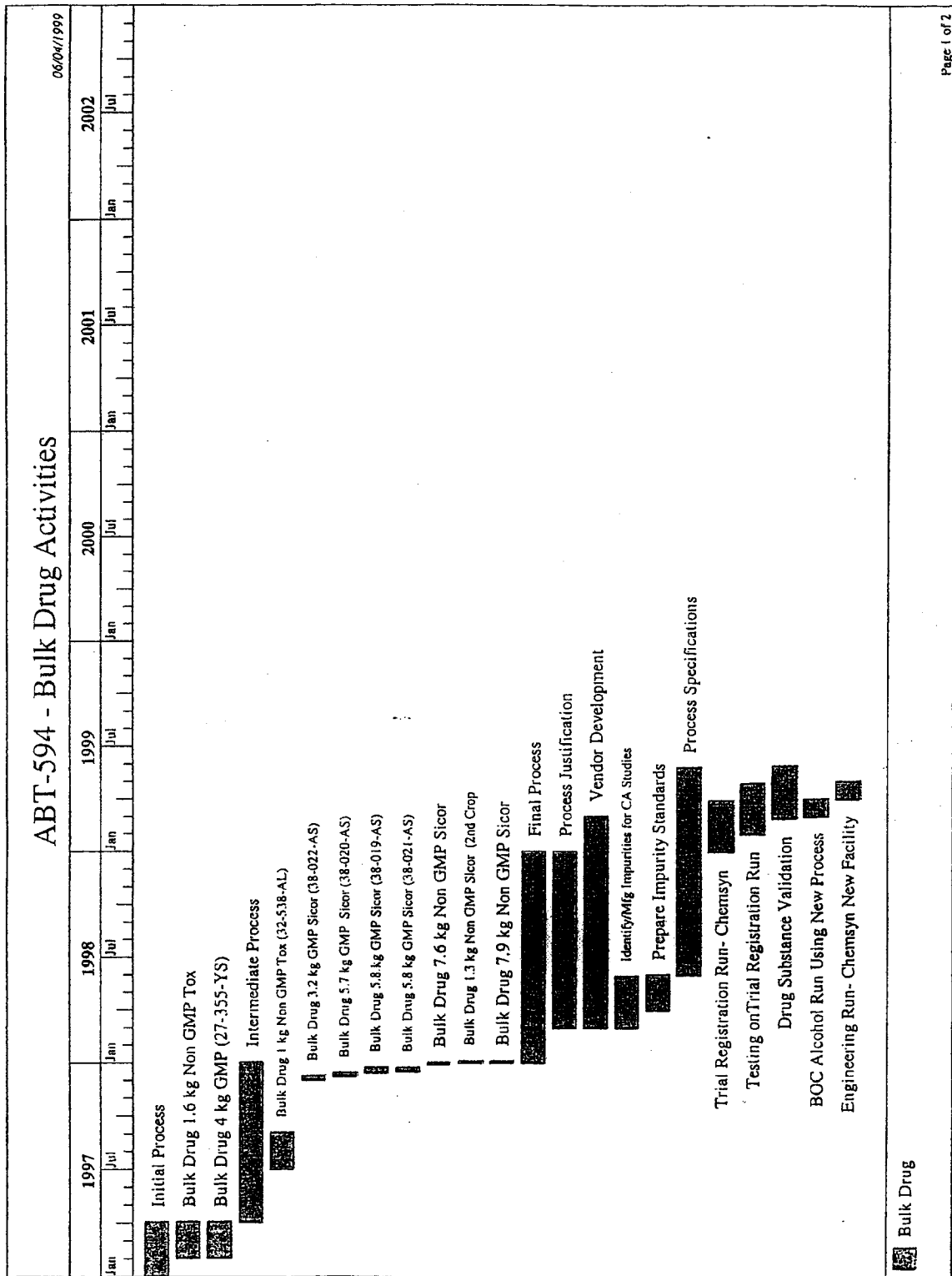
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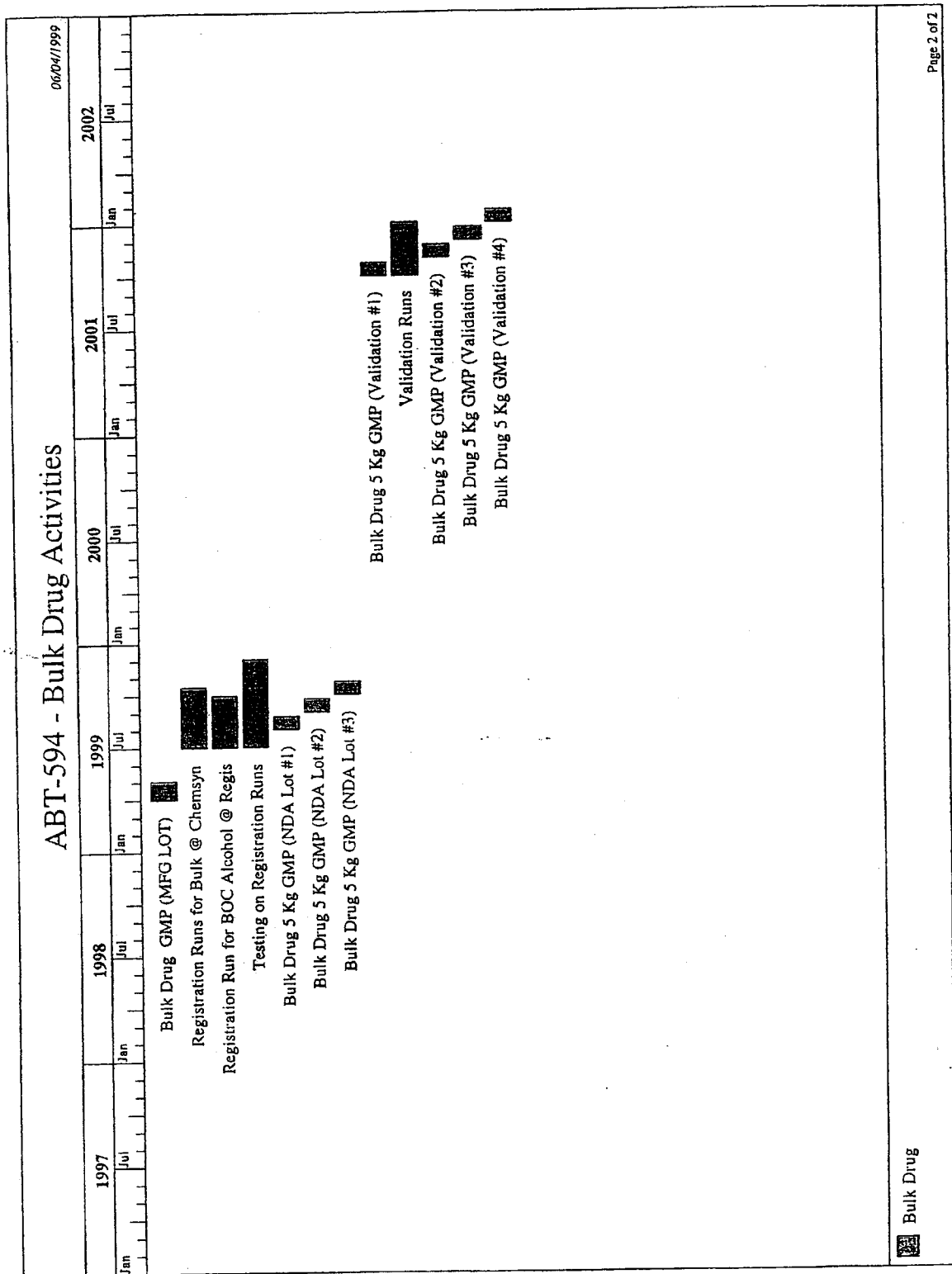
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Activity Listing

06/17/99

Description	Sponsor Bulk Drug		Project ABT-594		Indication Pain (General)	
	Version Plan		Project N GO 143010		Formulation Oral Solid	
	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Initial Process	NKAUD030	01/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Bulk Drug 4 kg GMP (27-355-YS)	NKAUWG02	02/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Bulk Drug 1.6 kg Non GMP Tox	NKAUWG05	02/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Intermediate Process	NKAUD031	04/01/1997	12/31/1997	12/31/1997	12/31/1997	C
Bulk Drug 1 kg Non GMP Tox (32-538-AL)	NKAUD012	07/01/1997	08/31/1997	08/31/1997	08/31/1997	C
Bulk Drug 3.2 kg GMP Sicor (38-022-AS)	NKAUWG08	12/01/1997	12/07/1997	12/07/1997	12/07/1997	C
Bulk Drug 5.7 kg GMP Sicor (38-020-AS)	NKAUWG09	12/08/1997	12/15/1997	12/15/1997	12/15/1997	C
Bulk Drug 5.8 kg GMP Sicor (38-019-AS)	NKAUD002	12/15/1997	12/22/1997	12/22/1997	12/22/1997	C
Bulk Drug 5.8 kg GMP Sicor (38-021-AS)	NKAUD003	12/17/1997	12/24/1997	12/24/1997	12/24/1997	C
Bulk Drug 7.6 kg Non GMP Sicor	NKAUD014	12/28/1997	01/02/1998	01/02/1998	01/02/1998	C
Bulk Drug 7.9 kg Non GMP Sicor	NKAUD015	12/31/1997	01/05/1998	01/05/1998	01/05/1998	C
Bulk Drug 1.3 kg Non GMP Sicor (2nd Crop)	NKAUD013	12/31/1997	01/05/1998	01/05/1998	01/05/1998	C
Final Process	NKAUD032	01/01/1998	12/31/1998	12/31/1998	12/31/1998	C
Identify/Mfg Impurities for CA Studies	NKAUD021	03/02/1998	05/29/1998	05/29/1998	05/29/1998	C
Process Justification	NKAUD023	03/02/1998	12/31/1998	12/31/1998	12/31/1998	C
Vendor Development	NKAUD020	03/02/1998	03/02/1999	03/02/1999	03/02/1999	C
Prepare Impurity Standards	NKAUD022	04/01/1998	06/03/1998	06/03/1998	06/03/1998	C
Process Specifications	NKAUD024	06/01/1998	05/27/1999	05/27/1999	05/27/1999	C
Trial Registration Run- Chemsyn	NKAUD025	01/01/1999	03/31/1999	03/31/1999	03/31/1999	C
Testing on Trial Registration Run	NKAUD026	02/01/1999	04/30/1999	04/30/1999	04/30/1999	C
Drug Substance Validation	NKAUD029	03/01/1999	05/30/1999	05/30/1999	05/30/1999	C
BOC Alcohol Run Using New Process	NKAUD034	03/02/1999	04/01/1999	04/01/1999	04/01/1999	C
Engineering Run- Chemsyn New Facility	NKAUD033	04/02/1999	05/02/1999	05/02/1999	05/02/1999	A
Bulk Drug GMP (MFG LOT)	NKAUD016	04/02/1999	05/02/1999	05/02/1999	05/02/1999	C
Registration Runs for Bulk @ Chemsyn	NKAUD027	07/01/1999	10/15/1999	10/15/1999	10/15/1999	A
Registration Run for BOC Alcohol @ Regis	NKAUD035	07/01/1999	09/29/1999	09/29/1999	09/29/1999	A
Testing on Registration Runs	NKAUD028	07/01/1999	11/30/1999	11/30/1999	11/30/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #1)	NKAUD017	08/01/1999	08/22/1999	08/22/1999	08/22/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #2)	NKAUD019	09/01/1999	09/22/1999	09/22/1999	09/22/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #3)	NKAUD018	10/01/1999	10/22/1999	10/22/1999	10/22/1999	A
Bulk Drug 5 Kg GMP (Validation #1)	NKAUD036	10/01/2001	10/22/2001	10/22/2001	10/22/2001	A
Validation Runs	NKAUD040	10/01/2001	01/01/2002	01/01/2002	01/01/2002	A
Bulk Drug 5 Kg GMP (Validation #2)	NKAUD037	11/01/2001	11/22/2001	11/22/2001	11/22/2001	A
Bulk Drug 5 Kg GMP (Validation #3)	NKAUD038	12/01/2001	12/22/2001	12/22/2001	12/22/2001	A

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Activity Listing

06/17/99

<i>Sponsor</i> Bulk Drug	<i>Project</i> ABT-594	<i>Indicatio</i> Pain (General)				
<i>Versio</i> Plan	<i>Project N</i> G0 143010	<i>Formulation</i> Oral Solid				
<i>Description</i>	<i>AN Num</i>	<i>Sty Start</i>	<i>Sty End</i>	<i>DB End</i>	<i>Sum End</i>	<i>Status Code</i>
Bulk Drug 5 Kg GMP (Validation #4)	NKAUD039	01/01/2002	01/22/2002	01/22/2002	01/22/2002	A

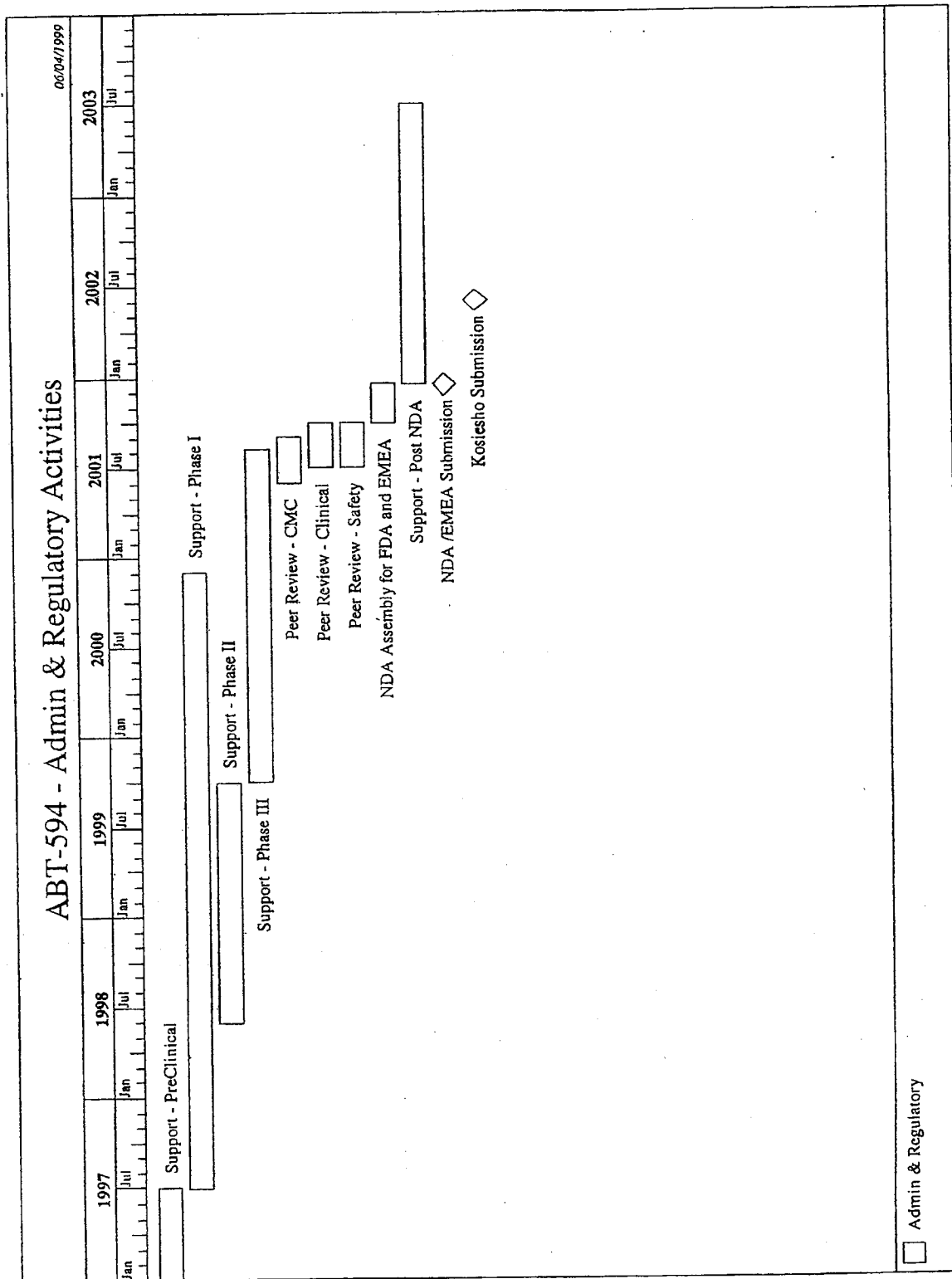
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ABBT 0019093



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Activity Listing

06/17/99

Sponsor Admin & Regulatory		Project	ABT-594		Indicatio	Pain (General)	
Version	Plan	Project N	GO 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Support - PreClinical		NKAZPS06	01/01/1997	07/01/1997	07/01/1997	07/01/1997	C
Support - Phase I		NKAZPS07	07/01/1997	12/01/2000	12/01/2000	12/01/2000	A
Support - Phase II		NKAZPS08	06/01/1998	09/30/1999	09/30/1999	09/30/1999	A
Support - Phase III		NKAZPS09	10/01/1999	08/06/2001	08/06/2001	08/06/2001	A
Peer Review - CMC		NKAZPS01	06/01/2001	08/31/2001	08/31/2001	08/31/2001	A
Peer Review - Safety		NKAZPS02	07/01/2001	10/01/2001	10/01/2001	10/01/2001	A
Peer Review - Clinical		NKAZPS03	07/01/2001	10/01/2001	10/01/2001	10/01/2001	A
NDA Assembly for FDA and EMEA		NKAZD003	10/01/2001	12/15/2001	12/15/2001	12/15/2001	A
NDA /EMEA Submission		NKAZD005	12/15/2001	12/15/2001	12/15/2001	12/15/2001	A
Support - Post NDA		NKAZPS10	12/15/2001	06/30/2003	06/30/2003	06/30/2003	A
Kosiesho Submission		NKAZD006	06/01/2002	06/01/2002	06/01/2002	06/01/2002	A

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Collicott Deposition Exhibit 4

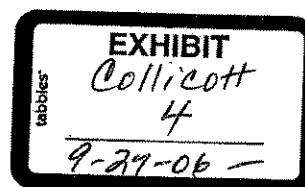
PART 1

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ABBOTT LABORATORIES
ABT-594
INVESTIGATIONAL NEW DRUG (IND)
ANNUAL REPORT
IND No. 55,293; IND No. 56,980
(Reporting Period March 21, 1999 - October 29, 1999)

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ABBOTT LABORATORIES
ABT-594
INVESTIGATIONAL NEW DRUG (IND)
ANNUAL REPORT
IND No. 55,293; IND No. 56,980
(Reporting Period March 21, 1999 - October 29, 1999)

Marilyn Collicott
Clinical Project Manager, Analgesia Venture

Date

Bruce McCarthy, M.D.
Associate Medical Director, Analgesia Venture

Date

Christopher Silber, M.D.
Venture Head, Analgesia Venture

Date

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ABT-594 Annual Report
 IND No. 55,293, IND No. 56,980
 (Reporting Period: March 21, 1999 to October 29, 1999)

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ABT-594 Annual Report
 IND No. 55,293, IND No. 56,980
 (Reporting Period: March 21, 1999 to October 29, 1999)

1

Introduction

Currently, there are two open IND applications for ABT-594, IND No. 55,293 (oral liquid formulation) and IND No. 56,980 (solid oral dosage form). This annual report for the reporting period March 21, 1999 to October 29, 1999 contains information in the safety database as of October 29, 1999 for IND No. 56,980. During this reporting period, no studies were conducted using the oral liquid formulation (IND No. 55,293). A summary of the ABT-594 clinical studies included in this annual report is presented in Table 1.

Table 1. Summary of ABT-594 Clinical Studies Included in This Annual Report			
Study Number	Study Type	Formulation	IND Status
Phase I Studies:			
M98-984	Bioavailability	Soft Elastic Capsule (SEC) Hard Gelatin Capsule (HGC)	IND No. 56,980
M99-043	Bioavailability	Soft Elastic Capsule (SEC) Hard Gelatin Capsule (HGC)	IND No. 56,980
M99-076	Ascending Doses	Hard Gelatin Capsule (HGC)	IND No. 56,980
Phase II Studies:			
M98-826	Osteoarthritis pain	Soft Elastic Capsule (SEC)	IND No. 56,980
M98-833	Neuropathic pain	Soft Elastic Capsule (SEC)	IND No. 56,980

ABT-594 Annual Report
IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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(a) INDIVIDUAL STUDY INFORMATION

(1) Phase I Studies

Protocol Number: M98-984

Title: The Bioavailability, Tolerability, and Effect of Food on a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects

Study Information: IND Study, Single Center
United States

Objective: To assess the bioavailability and tolerability of a hard gelatin capsule (HGC) relative to that of a soft elastic capsule (SEC) formulation of ABT-594 and the effect of food on the bioavailability and tolerability of the ABT-594 HGC formulation in healthy adult subjects.

Study Design: This was a Phase I, randomized, single center, open label, single-dose, four-period study in 24 healthy adult subjects. The study consisted of a two-week Screening Phase, a four-period Study Drug Administration Phase, and a Follow-Up Visit approximately 4-8 days after the last dose of study drug.

The Study Drug Administration Phase was comprised of two parts. Part I (Periods 1-3) was a randomized, three-period crossover to assess the bioavailability of a 100 mg total dose of a HGC formulation relative to that of an SEC formulation of ABT-594 under fasted conditions and the bioavailability of a 100 mg total dose of HGC formulation under fed conditions relative to that under fasted conditions. Part II was a randomized, single-dose administration to assess the tolerability of a 150 mg total dose of SEC and HGC under fasted conditions.

Subject Population: Healthy, non-nicotine using adult males and females between the ages of 18 and 45.

ABT-594 Annual Report
 IND No. 55,293, IND No. 56,980
 (Reporting Period: March 21, 1999 to October 29, 1999)

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Protocol: M98-984 (Continued)

Status	Start Date	Completion Date	Subjects Projected	Subjects Entered	Subjects Completed	Dropped Out
Completed	3/99	4/99	24	23	23	0

Population Demographics (n = 23)					
Age (years)	n (%)	Race	n (%)	Gender	n (%)
18-45	23 (100)	Caucasian	21 (91)	Male	17 (74)
		Black	2 (9)	Female	6 (26)

Study Results:

For C_{max} , the ABT-594 HGC 25 α g capsule formulation (Regimen B) was similar to the SEC 25 α g capsule formulation (Regimen A). The AUC central value was estimated to be 15% lower for the HGC formulation. In addition, the HGC formulation had a statistically significantly earlier mean T_{max} (by 1.6 hours) as compared to the SEC formulation.

Overall, the pharmacokinetics of ABT-594 after administration of the 25 μ g HGC formulation were fairly similar when the capsules were administered with or without food. However, the mean T_{max} was statistically significantly later (by 2.9 hours) for the nonfasting regimen compared to the fasting regimen.

The pharmacokinetic parameters of ABT-594 for the 100 μ g and 150 μ g doses of the HGC and SEC formulations appeared to be dose-proportional under fasting conditions.

ABT-594 Annual Report
IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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Protocol: M98-984 (Continued)

Overall, 70% of subjects reported at least one treatment-emergent adverse event. The most frequently reported ($\geq 5\%$ of subjects) treatment emergent adverse events in any of the five ABT-594 treatment regimens were dizziness, nausea, headache, vomiting, somnolence, asthenia, sweating, abdominal pain, abnormal vision, infection, abnormal thinking, dyspepsia, pallor and vasodilation. There were no serious adverse events reported and no safety concerns were identified during the Treatment Period.

A final study report is pending.

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IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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(a) INDIVIDUAL STUDY INFORMATION

(1) Phase I Studies

Protocol Number: M99-043

Title: The Bioavailability of a 75 mg Hard Gelatin Capsule
Formulation of ABT-594 in Healthy Adult Subjects

Study Information: IND Study, Single Center
United States

Objective: To assess the bioavailability of a 25 mg hard gelatin capsule (HGC) formulation of ABT-594 relative to that of a 25 mg soft elastic capsule (SEC) and relative to that of a 75 mg HGC in healthy adult subjects.

Study Design: This was a Phase I, randomized, open-label, single-dose, single-center, three-period complete crossover study in 24 healthy adult subjects. The study consisted of a 3-week Screening Phase, a three-period Study Drug Administration Phase, and a Follow-Up Visit approximately 4-8 days after the last dose of study drug. All doses were administered under fasted conditions.

On Day 1 of Period 1, 24 subjects were randomly assigned in equal numbers to receive one of the following regimens during the first dosing period:

Regimen A: Six 25 mg ABT-594 SECs under fasted conditions
Regimen B: Six 25 mg ABT-594 HGCs under fasted conditions
Regimen C: Two 75 mg ABT-594 HGCs under fasted conditions

For the remaining periods, subjects crossed-over and were administered the other regimens until all subjects received all regimens.

Subject Population: Healthy, non-nicotine using adult males and females between the ages of 18 and 45.

ABT-594 Annual Report
 IND No. 55,293, IND No. 56,980
 (Reporting Period: March 21, 1999 to October 29, 1999)

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Protocol: M99-043 (Continued)

Status	Start Date	Completion Date	Subjects Projected	Subjects Entered	Subjects Completed	Dropped Out
Completed	7/99	7/99	24	24	22	2*
* After the completion of dosing in Period 1, one subject prematurely terminated due to bacterial infection and one subject prematurely terminated due to anxiety.						

Population Demographics (n = 24)					
Age (years)	n (%)	Race	n (%)	Gender	n (%)
18-45	24 (100)	Caucasian	20 (83)	Male	20 (83)
		Black	4 (17)	Female	4 (17)

Study Results: The ABT-594 25 mg HGC formulation was bioequivalent to the ABT-594 25 mg SEC formulation with respect to AUC_{∞} and C_{max} because the 90% confidence intervals for evaluating bioequivalence were contained within the 0.80 to 1.25 range. The ABT-594 75 mg HGC formulation was also bioequivalent to the 25 mg HGC capsule formulation with respect to AUC_{∞} and C_{max} because the 90% confidence intervals for evaluating bioequivalence were contained within the 0.80 to 1.25 range.

The most frequently reported ($\geq 5\%$ of subjects) treatment-emergent adverse events in any of the three ABT-594 treatment regimens were dizziness, nausea, vomiting, headache, asthenia, pallor, somnolence, diarrhea, and abdominal pain. There were no serious adverse events reported and no safety concerns were identified during the Treatment Period.

A final study report is pending.

ABT-594 Annual Report
IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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(a) INDIVIDUAL STUDY INFORMATION

(1) Phase I Studies

Protocol Number: M99-076

Title: A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects

Study Information: IND Study, Single Center
United States

Objective: To evaluate the safety, tolerability, and pharmacokinetics of multiple ascending doses of twice daily dosing regimens of a hard gelatin capsule (HGC) formulation of ABT-594 in adult subjects in good health.

Study Design: This was a Phase I, randomized, double-blind, placebo-controlled parallel group, single-center study designed to involve approximately 120 adults to evaluate the safety, tolerability, and pharmacokinetic profile of ascending doses of twice daily dosing regimens of ABT-594 HGC formulation for 14 consecutive days. The study consisted of a 3-week Screening Phase and an 18-day Confinement Phase.

Approximately 120 subjects were to be assigned to 10 dosing groups (1-10) with 12 subjects in each group. The dosing groups were designed as follows:

Group 1: 75 mg or placebo
Group 2: 100 mg or placebo
Group 3: 125 mg or placebo
Group 4: 150 mg or placebo
Group 5: 175 mg or placebo
Group 6: 200 mg or placebo
Group 7: 250 mg or placebo
Group 8: 300 mg or placebo
Group 9: 375 or 450 mg or placebo
Group 10: 375, 450, 525 or 600 mg or placebo

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Protocol: M99-076 (Continued)

Study Design: Study drug was randomly assigned in a 3:1 ratio in each group such that nine subjects received ABT-594 and 3 subjects received placebo. All subjects received two fixed daily doses of ABT-594 or placebo 12 hours apart for 14 consecutive days. Dosing occurred under fed conditions.

Subject Population: Healthy, non-nicotine using adult males and females between the ages of 18 and 60.

Status	Start Date	Completion Date	Subjects Projected	Subjects Entered*	Subjects Completed*	Dropped Out*
Completed	8/99	11/99	120	108	86	22
* Through Group 9, preliminary data indicate that eighteen subjects prematurely terminated due to adverse events (including fourteen ^b for GI intolerance, two for rash, one for seizure-like symptoms, and one for tooth abscess), two subjects prematurely terminated due to the protocol specified stopping rule, one subject prematurely terminated for personal reasons, one for use of concomitant medication. ^b One adverse event of GI intolerance is currently not verified in the database but is included here.						

Population Demographics (n = 108)*					
Age (years)	n (%)	Race	n (%)	Gender	n (%)
18-60	108 (100)	Caucasian	74 (68)	Male	85 (79)
		Black	26 (24)	Female	23 (21)
		Other	8 (8)		
* Through Group 9					

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Protocol: M99-076 (Continued)

Study Results: Based upon the protocol specified stopping rule, dosing did not proceed beyond 375 mg BID (Group 9).

A complete clinical database is not yet available. Data collection has been completed through Group 4 (75 mg - 150 mg or placebo) and is summarized in Appendices B.1.1 and B.4.1. Data collection for Groups 5 and higher is currently underway and is not included in the database.

All data remains blinded.

A final study report is pending.

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(a) **INDIVIDUAL STUDY INFORMATION**

(2) **Phase II Studies**

Protocol Number: M98-826

Title: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee

Study Information: IND Study, Multicenter
 United States

Objective: To compare safety and efficacy of ABT-594 and ibuprofen to placebo in patients with pain associated with osteoarthritis.

Study Design: This was a Phase II, randomized, double-blind, placebo-controlled, active ibuprofen control, parallel group study. Eligible subjects were randomized to one of five treatment groups of 50 subjects each to receive either 25 α g, 50 α g, or 75 μ g of ABT-594 SEC twice daily, 400 mg ibuprofen three times daily, or matching placebo for 21 days with a morning dose on Day 22.

Subject Population: Adult subjects, between the ages of 18 to 75 years of age, with pain associated with primary Grade II or III osteoarthritis of the knee.

Status	Start Date	Completion Date	Subjects Projected	Subjects Entered	Subjects Completed	Dropped Out
Completed	12/98	6/99	250	256	197	59*
* Cumulative Premature Terminations by Treatment Group						

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Protocol: M98-826 (Continued)

	Placebo	Ibuprofen 400 mg TID	ABT-594 25 mg BID	ABT-594 50 mg BID	ABT-594 75 mg BID
Prematurely Terminated	13 (24%)	7 (14%)	15 (31%)	11 (23%)	13 (25%)
Adverse Event	3 (5%)	2 (4%)	5 (10%)	4 (8%)	6 (11%)**
Non-compliance	3 (5%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)
Lost to Follow-Up	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)
Lack of Efficacy	7 (13%)	3 (6%)	8 (16%)	5 (10%)	3 (6%)
Other	0 (0%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)

** Includes one subject with onset of adverse event occurring prior to dosing.

Population Demographics (n = 256)					
Age (years)	n (%)	Race	n (%)	Gender	n (%)
18-65	159 (62)	Caucasian	239 (93)	Male	97 (38)
≥65	97 (38)	Black	14 (5)	Female	159 (62)
		Other	3 (1)		

**Preliminary
 Study Results:**

ABT-594 at 25, 50, or 75 mg BID, did not differ significantly from placebo in the protocol specified primary (daily pain intensity four-point categorical scale) and secondary (daily pain intensity visual analog scale, global evaluation of study drug, pain intensity four-point categorical and visual analog scales, WOMAC Index Version VA 3.0, rescue medication use) variables. ABT-594 75 mg BID was, however, numerically better than placebo as measured by all WOMAC subscale scores and several additional scales.

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Protocol: M98-826 (Continued)

The most frequently reported ($\geq 5\%$ of subjects) treatment-emergent adverse events in any of the three ABT-594 treatment groups were abdominal pain, asthenia, headache, infection, diarrhea, dyspepsia, nausea, vomiting, dizziness, pain, increased cough and pharyngitis. Statistically significant differences were observed between the placebo treatment group and the ABT-594 50 mg BID and 75 mg BID treatment group with respect to the incidence of asthenia ($p = 0.044$) and the incidence of nausea ($p = 0.003$), respectively. A decrease in the incidence of nausea, vomiting and dizziness among ABT-594 treated-subjects was noted over time. There were no serious adverse events reported in ABT-594 treated subjects. In addition, the proportion of subjects that prematurely discontinued due to adverse events did not differ significantly among treatment groups. During the 22-day Treatment Period, no safety concerns were identified.

The final study report is pending.

Collicott Deposition Exhibit 4

PART 3

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(b) SUMMARY INFORMATION

**(2) IND Safety Reports [21 CFR 312.33 (b) (2)] for the Time Period March 21, 1999
Through October 29, 1999**

For this reporting period, there were no expedited IND Safety Reports filed under IND
Nos. 56,980 and 55,293.

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(b) SUMMARY INFORMATION

**(3) Subjects Who Died During Participation in the Investigation
[21 CFR 312.33 (b) (3)]**

For this reporting period, one death occurred. The narrative for this event is presented below.

Investigator: Schnitzer

Patient Number: 1040

A 60-year old Caucasian male randomized to ibuprofen experienced a fatal myocardial infarction (COSTART Term: infarct myocardial) on Study Day 12 (4 days post-treatment). The subject had a medical history of aortic valve disease, arteriosclerosis (1996), shortness of breath related to cigarette smoking since 1998 (1½ packs/day), elevated triglyceride level of 358 mg/dL (normal range 58-260 mg/dL) on Day 8 and non-specific ST and T wave abnormalities on both the Screening and Baseline Visit ECG which were deemed not clinically significant by the investigator. The subject weighed 271 pounds and was 71 inches tall. On Study Day 12 (four days post-treatment), the subject was dead on arrival at a local hospital. Details surrounding the event are unknown. The death certificate indicated the cause of death was myocardial infarction due to coronary artery disease. Concomitant medications were K-dur[®] and Lasix[®]. The investigator considered the event unrelated to study drug and noted coronary artery disease as an alternative etiology. The blind was broken by the sponsor to determine reportability requirements to the FDA.

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(b) SUMMARY INFORMATION

(4) Subjects or Patients Who Prematurely Terminated During the Course of the Investigation due to an Adverse Event [21 CFR 312.33 (b) (4)]

Appendix B.4.1 presents the adverse events leading to study discontinuation for healthy volunteer subjects in current Phase I studies as of October 29, 1999. ABT-594 SEC was used in two of the three Phase I studies (M98-984, M99-043). ABT-594 HGC was used in all three Phase I studies (M98-984, M99-043, M99-076). BLINDED premature discontinuation information due to adverse events is provided for Study M99-076, Groups 1 through 4. Adverse event information is summarized from all three Phase I studies conducted during this reporting period.

Appendix B.4.2 presents the adverse events leading to study discontinuation for subjects in Phase II Studies as of October 29, 1999. ABT-594 SEC was used in the two Phase II studies (M98-826, M98-833). Adverse event information is summarized from both Phase II studies conducted during this reporting period.

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(b) SUMMARY INFORMATION

(5) Information Obtained Pertinent to the Understanding of the Drug's Actions [21 CFR 312.33 (b) (5)]

Pharmacokinetic results are summarized below for Studies M98-984 and M99-043. Study M99-076 remains blinded and pharmacokinetic results are not yet available. The data for M98-826 is preliminary and will not be included in this report. Pharmacokinetic data was not collected for Study M98-833.

M98-984

The Bioavailability, Tolerability and Effect of Food on a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects

Objectives: The objectives of this study were: 1) to assess the bioavailability and tolerability of a hard gelatin capsule (HGC) formulation of ABT-594 relative to that of a soft elastic capsule (SEC) formulation of ABT-594; 2) to determine the effect of food on the bioavailability and tolerability of the ABT-594 HGC formulation; and 3) to assess the tolerability and pharmacokinetics of a 150 mcg dose of the HGC and SEC formulations under fasting conditions in healthy adult subjects. This summary focuses on the pharmacokinetics of ABT-594.

Study Design and Dose Administration: This was a Phase I, single-dose, open-label, single-center, randomized, four-period study. The study consisted of two parts.

Part I (Periods 1 through 3) was a randomized, three-period crossover. The regimens for Part I were defined as: Regimen A – Four 25 µg ABT-594 SECs (100 µg total dose) administered under fasting conditions, Regimen B – Four 25 µg ABT-594 HGCs (100 mcg total dose) administered under fasting conditions and Regimen C – Four 25 µg ABT-594 HGCs (100 µg total dose) administered under nonfasting conditions.

Part II (Period 4) was a randomized, single-dose administration. The regimens for Part II were defined as: Regimen D – Six 25 µg ABT-594 SECs (150 µg total dose) administered under fasting conditions and Regimen E – Six 25 µg ABT-594 HGCs (150 µg total dose) administered under fasting conditions.

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The capsules taken for all regimens were ingested with 250 mL of water. There was a seven-day interval between dosing days of consecutive periods. For subjects dosed under nonfasting conditions (Regimen C), a 872 Kcal breakfast (53.8% calories from fat), was served approximately 30 minutes before dosing.

Subjects: Healthy adult male and female subjects ($N = 23$) were enrolled in the study. All 23 subjects (17 males and 6 females) who participated completed the study. Of the 23 subjects who completed the study, 21 were Caucasian and two were Black. For these subjects, the mean age was 31.7 years (range: 20 to 45 years), the mean weight was 74.5 kg (range: 55.5 to 90 kg) and the mean height was 171.7 cm (range: 146.5 to 186 cm).

Sample Collection: In each period, blood samples were collected at the following intervals relative to Day 1 dosing: predose (0 hour) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36 and 48 hours after dosing. For subjects dosed under nonfasting conditions (Regimen C), all predose samples were obtained after breakfast had been eaten, but prior to morning dosing.

Pharmacokinetic and Statistical Analyses: The pharmacokinetic parameters of ABT-594 were calculated using noncompartmental methods. These included: T_{lag} , T_{max} , C_{max} , the elimination rate constant (β), half-life ($t_{1/2}$), the area under the plasma concentration-time curve from time zero to time of the last measurable concentration (AUC_t), the area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) and the apparent total clearance (CL/F).

Results: All available data for the 23 subjects who received study drug were included in the analyses. The mean \pm SD pharmacokinetic parameters of ABT-594 after administration of each of the five regimens are shown in the following table.

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Pharmacokinetic Parameters	Regimens				
	A: 100 µg SEC Fasting (N = 23)	B: 100 µg HGC Fasting (N = 23)	C: 100 µg HGC Nonfasting (N = 23)	D: 150 µg SEC Fasting (N = 11)	E: 150 µg HGC Fasting (N = 12)
$T_{1/2}$ (h)	1.2 ± 0.8	0.9 ± 0.3	2.0 ± 1.1 [†]	0.8 ± 0.5	0.6 ± 0.2
T_{max} (h)	5.6 ± 1.7	4.0 ± 1.5 [*]	6.9 ± 2.3 [†]	5.5 ± 0.9	3.8 ± 1.1
C_{max} (ng/mL)	0.47 ± 0.19	0.48 ± 0.17	0.43 ± 0.17	0.71 ± 0.13	0.82 ± 0.14
$AUC_0-\infty$ (ng•h/mL) [†]	5.4 ± 2.9	4.6 ± 2.7	4.4 ± 2.4	9.9 ± 2.2	9.0 ± 2.1
AUC_{0-t} (ng•h/mL)	6.6 ± 3.1	5.9 ± 3.0	5.6 ± 2.7	10.7 ± 2.3	9.7 ± 2.3
$t_{1/2}$ (h) [‡]	8.0 ± 3.3	7.4 ± 3.7	7.4 ± 3.3	6.9 ± 2.2	5.6 ± 1.3
CL/F (L/h) [†]	20.1 ± 11.9	24.1 ± 18.0	23.4 ± 14.2	14.6 ± 2.8	16.4 ± 3.9
[*] Statistically significantly different from Regimen A (ANOVA, $p < 0.05$). [†] Statistically significantly different from Regimen B (ANOVA, $p < 0.05$). [‡] Evaluations of $t_{1/2}$ were based on statistical tests for β . [†] Parameter was not tested statistically.					

For the two one-sided tests procedure based on analyses of log-transformed $AUC_{0-\infty}$ and C_{max} , the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate [†]	90% Confidence Interval
A vs. B	C_{max}	0.436	0.434	1.005	0.843 - 1.199
	$AUC_{0-\infty}$	4.96	5.84	0.849	0.665 - 1.084
[*] Antilogarithm of the least squares means for logarithms. [†] Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.					

To evaluate the effect of food on the 25 µg HGC formulation, the point estimates and 95% confidence intervals for relative bioavailability are listed in the following table.

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Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate†	95% Confidence Interval
C vs. B	C _{max}	0.394	0.436	0.904	0.732 - 1.117
	AUC _∞	5.02	4.96	1.013	0.756 - 1.358
* Antilogarithm of the least squares means for logarithms.					
† Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.					

Conclusions: For C_{max}, the ABT-594 HGC 25 µg capsule formulation (Regimen B) was similar to the SEC 25 µg capsule formulation (Regimen A). The AUC central value was estimated to be 15% lower for the HGC formulation. In addition, the HGC formulation had a statistically significantly earlier mean T_{max} (by 1.6 hours) as compared to the SEC formulation.

Overall, the pharmacokinetics of ABT-594 after administration of the 25 µg HGC formulation were fairly similar when the capsules were administered with or without food. However, the mean T_{max} was statistically significantly later (by 2.9 hours) for the nonfasting regimen compared to the fasting regimen.

The pharmacokinetic parameters of ABT-594 for the 100 µg and 150 µg doses of the HGC and SEC formulations appeared to be dose-proportional under fasting conditions.

M99-043

The Bioavailability of a 75 µg Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects

Objective: The objective of this study was to assess the bioavailability of a 25 µg hard gelatin capsule (HGC) formulation of ABT-594 relative to that of a 25 µg soft elastic capsule (SEC) formulation and relative to that of a 75 µg HGC formulation in healthy adult subjects.

Study Design and Dose Administration: This was a Phase I, single-dose, fasting, open-label, randomized, three-period, crossover study. The regimens used in this study were defined as follows: Regimen A, six 25 µg ABT-594 SECs (150 µg total dose) under fasting conditions; Regimen B, six 25 µg ABT-594 HGCs (150 µg total dose) under fasting conditions; and Regimen C, two 75 µg HGCs (150 µg total dose) under fasting conditions. Each regimen was administered with 250 mL of water after an

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approximate ten-hour fast and four hours prior to lunch. A washout interval of seven days separated dosing days of consecutive periods.

Subjects: Healthy adult male and female subjects ($N = 24$) were enrolled in the study. A total of 22 of the subjects (18 males and 4 females) completed all three periods of the study and were included in the summary calculations and statistical analyses. Of the 22 subjects who completed the study, 18 were Caucasian and four were Black. The mean age was 29.1 years (range: 18 to 45 years), the mean weight was 78.7 kg (range: 62 to 96 kg) and the mean height was 176.5 cm (range: 161.5 to 190.5 cm).

Sample Collection: Blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36 and 48 hours after the dose in each study period.

Pharmacokinetic and Statistical Analyses: The pharmacokinetic parameters of ABT-594 were calculated using noncompartmental methods. These included: T_{max} , C_{max} , the elimination rate constant (β), half-life ($t_{1/2}$), the area under the plasma concentration-time curve from time zero to time of the last measurable concentration (AUC_t), the area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) and the apparent oral clearance (CL/F).

Results: All available data for the 22 subjects who completed the study were included in the analyses. The mean \pm SD pharmacokinetic parameters of ABT-594 after administration of each of the three regimens are shown in the following table.

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Pharmacokinetic Parameters	Regimens [‡]		
	A 25 µg SECs (N = 22)	B 25 µg HGCs (N = 22)	C 75 µg HGCs (N = 22)
T _{max} (h)	6.4 ± 2.2	3.9 ± 1.0*	3.6 ± 1.2
C _{max} (ng/mL)	1.19 ± 0.27	1.22 ± 0.23	1.26 ± 0.22
AUC _t (ng•h/mL)	18.7 ± 4.4	16.5 ± 2.9*	17.2 ± 3.1
AUC _∞ (ng•h/mL)	19.9 ± 4.6	17.7 ± 2.9*	18.3 ± 3.1
t _{1/2} (h) [†]	9.8 ± 1.7	9.8 ± 1.9	10.1 ± 2.3
CL/F (L/h) [†]	7.9 ± 1.5	8.7 ± 1.6	8.4 ± 1.3
[‡] Regimen A: Six 25 µg SECs (150 µg total dose) under fasting conditions. Regimen B: Six 25 µg HGCs (150 µg total dose) under fasting conditions. Regimen C: Two 75 µg HGCs (150 µg total dose) under fasting conditions. * Statistically significantly different from Regimen A (ANOVA, p < 0.05). † Parameter was not tested statistically.			

For the two one-sided tests procedure based on analyses of log-transformed AUC_∞ and C_{max}, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate [†]	90% Confidence Interval
B vs. A	C _{max}	1.026	0.951 – 1.108
(25 µg HGC vs. 25 µg SEC)	AUC _∞	0.887	0.840 – 0.937
C vs. B	C _{max}	1.038	0.961 – 1.120
(75 µg HGC vs. 25 µg HGC)	AUC _∞	1.037	0.982 – 1.095
[†] Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.			

Conclusions: The ABT-594 25 µg HGC formulation (Regimen B) was bioequivalent to the ABT-594 25 µg SEC formulation (Regimen A) with respect to AUC_∞ and C_{max} because the 90% confidence intervals for evaluating bioequivalence were contained within the 0.80 to 1.25 range. The ABT-594 75 µg HGC formulation (Regimen C) was also bioequivalent to the 25 µg HGC capsule formulation (Regimen B) with respect to AUC_∞ and C_{max} because the 90% confidence intervals for evaluating bioequivalence were contained within the 0.80 to 1.25 range.

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(b) SUMMARY INFORMATION

(6) Preclinical Studies Completed or in Progress During the Reporting Period
[21 CFR 312.33 (b) (6)]

In Vitro Studies

Since the March 1999 IND update, ABT-594 has been used as a reference compound in a few *in vitro* experiments to characterize newer compounds. These experiments are a part of ongoing studies to identify potential back-up compounds to ABT-594.

ABT-594 was used as a reference compound in the primary *in vitro* functional analysis of new compounds. This assay uses a FLIPR apparatus to measure the effect of compounds on modulation of Ca^{2+} dynamics. Stable cell lines expressing recombinant nAChRs were previously established by co-transfecting human HEK cells with the indicated pairs of receptor subunits. The cell lines K177, K414, KRT44, and KRT6, which express recombinant human $\alpha 4\beta 2$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, and $\alpha 4\beta 4$ nAChRs, respectively, were used in these studies. Combined with previous data, mean EC_{50} values were 0.50 mM, 2.8 mM, 0.12 mM, and 0.016 mM for the $\alpha 4\beta 2$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, and $\alpha 4\beta 4$ nAChRs, respectively.

ABT-594 was also used as a reference compound for electrophysiologic evaluation of human nAChR pharmacology in *Xenopus* oocytes. Combined with previous data, the mean EC_{50} and Hill coefficient values were 0.14 mM and 1.1 at h- $\alpha 4\beta 2$; 0.60 mM and 1.0 at h- $\alpha 3\beta 2$; 0.64 mM and 1.4 at h- $\alpha 3\beta 4$; 7.8 mM and 2.8 at h- $\alpha 7$ nAChR, respectively.

Toxicology Studies

A summary of ongoing ABT-594 preclinical toxicology studies which occurred during this reporting period are listed in Table 2. Data is not yet available for these studies.

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Table 2. Summary of Ongoing ABT-594 Preclinical Toxicology Studies			
Protocol Number	Title	Start Date	Expected End Date
TC 98-082	Twelve-Month Oral Toxicity Study Of Abbott-165594 Tosylate in Cynomolgus Monkeys	6/98	12/99
TD98-131	Two-Year Oral Gavage Carcinogenicity Study of Abbott-165594 Tosylate in Mice	11/98	9/01
TA98-132	Two-Year Oral Gavage Carcinogenicity Study of Abbott-165594 Tosylate in Rats	9/98	11/01
TA98-161	Study of the Effects of Orally Administered Abbot-165594 on Pre- and Postnatal Development, Including Maternal Function, in Rats (Segment III DART)	1/99	1/00

A single ABT-594 pre-clinical metabolism study was conducted during this reporting period. Individual study information follows.

Metabolism

Report No.: R&D/99/357

Title: Metabolism and excretion of [³H]Abbott-165594 following oral administration to mice

Study Summary: The metabolism and excretion of [³H]Abbott-165594 was studied in male and female Crl:CD-1[®]/ICR mice following a single 1 mg/kg oral dose of the drug. Urine and feces were collected daily for three days. Plasma samples were obtained at selected time points up to 24 hours.

An oral radioactive dose of Abbott-165594 was well absorbed. The mean C_{max} for total plasma radioactivity (78.4 ng Eq/mL) was reached within four hours after dosing and then declined to 35.8, 6.5 and 2.9 ng Eq/mL at 6, 12 and 24 hours, respectively. The average AUC₀₋₂₄ was 561.8 ng Eq•h/mL. No obvious sex related differences were observed.

Peak plasma concentrations of Abbott-165594 in male (39.2 ng Eq/mL) and female (32.9 ng Eq/mL) mice occurred at 4 and 1 hours post dose, respectively. Corresponding AUC₀₋₂₄ values in males and females were 214.3 ng Eq•h/mL and 147.3 ng Eq•h/mL.

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Major plasma metabolites, expressed as mean AUC_{0-24} values, were identified as the ring opened COOH metabolite (M-1; 128.8 ng Eq•h/mL), the carbamoyl glucuronide of parent drug (M-8; 22.3 ng Eq•h/mL) and the N-acetylated ring opened COOH metabolite (M-6; 20.3 ng Eq•h/mL).

The majority of the radioactive dose in males and females was excreted into the urine. An average of 69.8% of the dose was recovered in urine (including cagewash) and 20.3% found in the feces over the duration of the three-day study. The mean total recovery of radioactivity was about 90%.

The major radioactive component in the 0-48 hour urine was unchanged parent drug which represented 33.8% and 52.3% of the administered dose in males and females, respectively. Major urinary metabolites in both sexes were M-1 (10.8% of the dose) and M-6 (2.5% of the dose). An apparent sex-related difference was also noted in that urinary level of the ring opened OH metabolite (M-14) in males (4.5% of the dose) was about 10-fold higher than that in females (0.4% of the dose). Unidentified metabolites accounted for about 10% of the dose. There were no apparent sex-related differences in fecal metabolic profiles obtained from male and female mice. The data indicate that oral doses of [3H]Abbott-165594 are well absorbed, rapidly excreted into the urine and not extensively metabolized in mice.

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(b) SUMMARY INFORMATION

(7) Significant Manufacturing or Microbial Changes [21 CFR 312.33 (b) (7)]

Significant Manufacturing or Microbial Changes

During the reporting period, there were no significant manufacturing or microbial changes in the formulation of ABT-594.

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(c) GENERAL INVESTIGATIONAL PLAN [21 CFR 312.33 (c)]

General Investigational Plan including Rationale for ABT-594 Use in Analgesia

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs); 2) opioids; 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]); and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. Opioids are used for moderate to severe pain and include such analgesics such as morphine. Clinically significant physical dependence and tolerance to analgesia may occur in patients receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of analgesic effect because of their mechanism of action and the requirement for dose titration. Acetaminophen is useful only for mild pain and tramadol is not indicated for severe pain. Therefore a class of compounds with a broad spectrum of activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs, and other currently available analgesics would represent an important advance in pain relief.

ABT-594 is a non-opioid, non-NSAID analgesic. It is a novel neuronal nicotinic acetylcholine receptor (nAChR) ligand that is 30- to 100- fold more potent than morphine. ABT-594 demonstrates comparable analgesic activity to morphine in treating moderate to severe pain in several well characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

Three Phase I studies were completed during this reporting period. These studies have provided information regarding the bioavailability and tolerability of the soft elastic capsule (SEC) vs. the hard gelatin capsule (HGC) in the solid oral formulation (M98-984, M99-043) and the safety, tolerability and pharmacokinetics of ascending twice-daily doses of ABT-594 HGC (M99-076).

ABT-594 Annual Report
 IND No. 55,293, IND No. 56,980
 (Reporting Period: March 21, 1999 to October 29, 1999)

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Two Phase II studies were completed during this reporting period. Study M98-826 provided information regarding safety, efficacy and pharmacokinetics in subjects with pain due to osteoarthritis of the knee. Study M98-833 provided information regarding safety and efficacy in subjects with painful distal polyneuropathy. ABT-594 was well-tolerated in both studies.

Based on information collected from the above mentioned Phase I and II studies, the general investigational plan for ABT-594 for the period of October 30, 1999 through October 29, 2000 allows for assessment of tolerability of higher doses and additional Phase II studies of ABT-594. The plan is outlined in Table 3 below.

Table 3. Planned Clinical Studies				
Study Number	Study Type	Phase	Planned Number of Subjects	Estimated Start Date
M99-120	Titration	I	20	11/99
M99-114	Neuropathic Pain	II	320	4/00
M99-115	Osteoarthritis Pain	II	575	4/00

Planned Phase I Study

Study M99-120 is a randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of escalating doses of ABT-594 BID in adult subjects in general good health. The hard gelatin capsule (HGC) formulation will be used for this study. The study, conducted at a single site, will include 20 subjects who will be randomized in a 3:1 ratio such that 15 receive ABT-594 and five received placebo. Subjects will receive two fixed daily doses, 12 hours apart, for 18 consecutive days under fed conditions. Daily doses of ABT-594 may vary among subjects. All subjects will start with a dose of 75 µg BID. Dose escalation days are Study Days 3, 5, 7, 9, and 14. The dose is planned to be escalated by 75 µg on each dose escalation day. The planned dose escalation schedule is 75 µg BID on Study Days 1 and 2, 150 µg BID on Study Days 3 and 4, 225 µg BID on Study Days 5 and 6, 300 µg BID on Study Days 7 and 8, 375 µg BID on Study Days 9 through 13, and 450 µg BID on Study Days 14-18. Escalation of the dose for any one subject will be postponed if that subject fails to meet predetermined dose escalation criteria. Results from this study will guide dose selection for the planned Phase II studies.

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(Reporting Period: March 21, 1999 to October 29, 1999)

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Planned Phase II Studies

M99-114 is a randomized, double-blind, placebo-controlled comparison of the safety and efficacy of ABT-594 to placebo in patients with painful diabetic polyneuropathy. This is a multi-center study in which an estimated 320 patients will be randomly assigned to receive either ABT-594 (HGC) BID or placebo for 42 days. Three ABT-594 dosages will be used for this study. Actual dosage strengths have yet to be determined.

M99-115 is a randomized, double-blind, placebo-controlled comparison of the safety and efficacy of ABT-594 and ibuprofen to placebo in patients with pain associated with osteoarthritis of the knee. This is a multi-center study in which an estimated 575 patients will be randomized to receive either ABT-594 (HGC) BID, ibuprofen 800 mg TID, or placebo for 42 days. Three ABT-594 dosages will be used for this study. Actual dosage strengths have yet to be determined. Acetaminophen will be provided as rescue medication.

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(d) INVESTIGATOR'S BROCHURE [21 CFR 312.33 (d)]

An updated Clinical Investigator's Brochure, Edition No. 3 (8/26/98) was submitted in September, 1998.

No modifications have been made to the investigator's brochure submitted in September, 1998. The investigator's brochure is currently being updated and will be submitted in the future.

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(Reporting Period: March 21, 1999 to October 29, 1999)

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(e) SIGNIFICANT PHASE I PROTOCOL MODIFICATIONS
[21 CFR 312.33 (e)]

There have been no unreported significant Phase I protocol modifications for clinical studies conducted under IND Nos. 56980 and 55,293 during this reporting period.

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IND No. 55,293, IND No. 56,980
(Reporting Period: March 21, 1999 to October 29, 1999)

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(f) SIGNIFICANT FOREIGN MARKETING INFORMATION
[21 CFR 312.33 (f)]

ABT-594 is not currently marketed in any country, nor has it been withdrawn or suspended from marketing in any country.

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ABBT335569

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(g) OUTSTANDING BUSINESS [21 CFR 312.33 (g)]

At this time, there is no outstanding business with respect to either IND No. 55, 293 or IND No. 56, 980 for which the sponsor requests a response from the Agency.

D461\FILENAME]

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ABBT335570

Collicott Deposition Exhibit 7

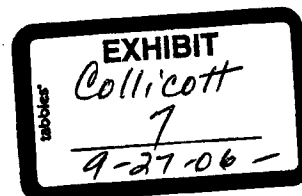
P's Exhibit CE

June 2000
ABT-594 Project Status Report

Monthly Highlights

Key Progress Gauges - June Accomplishments			Target Date	Status
<ul style="list-style-type: none"> Experimental placebo manufacturing run prepared at PPD's Puerto Rico Manufacturing Plant (AHP1) in the Potent Drug Module. Special thanks to Serafin Torres and the API plant personnel, and PARD team members Rhonda Peck, Erskine Hilyer and Ji Zhou for their commitment and long hours! Enrollment in M99-114 is slower than planned and is under scrutiny by team personnel. (See July Progress Gauges below.) 				
Begin testing for release and stability initiation of the 3 NDA lots of drug substance			6/5	Incomplete - Delay due to specification system issues (see below) Revised Target: 7/21
Issue new drug substance test document			6/5	Incomplete - Delay due to issues surrounding new specification documentation system. Revised Target: 7/21
Complete Development Plan preparation meetings			6/16	Complete
90 patients enrolled M99-114			6/25	Incomplete - 73 enrolled as of 6/30
2/3 of sites actively enrolling patients M99-114			6/25	Incomplete - 18 / 29 sites actively enrolling, 24 / 29 sites actively screening
Obtain validated results for ICH Category 1 solvent DCE in 594 clinical drug substance lots and starting material			6/25	In Process
Discovery Project Team to identify 3 potential follow-on compounds for advanced preclinical characterization			6/30	Complete
Develop cholinergic channel modulator scientific franchise strategy			6/30	Complete
Complete preparation for experimental capsule manufacturing run at AHP1 (900) to assess environmental/employee exposure			6/30	Complete
July Projections			Target Date	Status
Contact all M99-114 investigators to determine enrollment obstacles			7/5	
Review early terminations and Adverse Event profile to determine strategic options to address slow enrollment			7/12	
Finalize recommendations and initiate recommended strategies			7/21	
Issue new drug substance test document			7/21	
Begin testing for release and stability initiation of the 3 NDA lots of drug substance			7/21	
90 patients enrolled M99-114			7/31	
Schedule active capsule experimental manufacturing run at AHP1 for 8/00			7/31	

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Collicott Deposition Exhibit 8

P's Exhibit HQ

ABT-594 2001 Update Clinical Studies

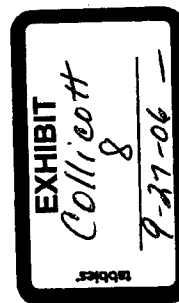
Project/Protocol Title Start (1st Dose) End (Last Dose) Subjects Sites #EVR Sites EVR Countries Comments

G0 143.010
Phase III Studies All Phase III work moved out to 2002

G0 143.010
Phase I Studies Most Phase I work moved out to 2002

TBD	fMRI / human pain model	2/01	9/01	12	1	1	1	Drug supply only: no DM or slats analysis
TBD	Human Metabolism 3H	9/01	9/01	5	1	0	0	Drug supply only: no DM or slats analysis
TBD	GI Absorption	9/01	12/01	24	1	0	0	

Phase IIb Studies	Painful Diabetic Neuropathy	04/00	04/01	320	30	0	0	4 arms, placebo-controlled
M99-114								5 arms, placebo-controlled, ibuprofen comparator, 7-week duration, all CRFs in house 8-10 months after study start.
M99-115	Osteoarthritis Study	01/01	10/01	575	40	0	0	5 arms, placebo-controlled, ibuprofen comparator, single dose, all CRFs in house after start + 3 months
TBD	Molar Extraction Study	TBD	Start + 2 mos	120	1	0	0	



07/08/2000 m.lamissen
2001, Clinical Studies
ABT594 Assumption Attachments, 08-18-00.xls

**ABT-594 2001 Update
Supplemental Assumptions**

<u>Protocol #</u>	<u>Genetic Sampling</u>	<u>ACPRU</u>	<u>PK</u>	<u>Subject on Drug</u>	<u>PK Samples/Patient</u>	<u>Date of Last Sample</u>
-------------------	-----------------------------	--------------	-----------	----------------------------	-------------------------------	--------------------------------

All Phase III work moved out to 2002

Most Phase I work moved out to 2002

TBD	N	N	Y	12	TBD	09/01
TBD	N	N	Y	5	10 (U)	09/01
TBD	N	Y	Y	24	TBD	12/01

M99-114	Y	N	Y	240		
M99-115	Y	N	Y	480	2 + (P)	TBD
TBD	Y	N	Y	96	7 (P)	TBD

07/09/2000 m.blumstein
2001, Supplemental Assumptions
ABT594 Assumption Attachments, 06-10-00.xls

Collicott Deposition Exhibit 11

P's Exhibit CR



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
08/31/2000 12:03 PM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
cc Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject M99-114 Extension letter

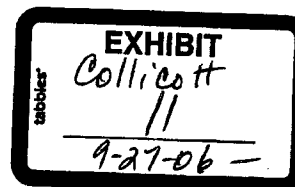
Chris -

Here's a copy of the extension letter for your review. Bruce has seen it and his comments have been incorporated.....mc



extension letter.doc

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ABBT241301

August 31, 2000

<Investigator Name>
<Address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr.:

I am pleased to inform you that the enrollment period for study M99-114 has been extended. The last day for randomization will be March 2, 2001. If we reach our target enrollment before that date the study will be ended at the time when 320 subjects are randomized.

While it may now seem that we have a bit of breathing room, in actuality we don't. The holidays are fast approaching - a time when recruitment and enrollment slows down considerably. We will, in effect, be losing approximately 2 months of our enrollment extension to the holiday season. That will leave us with just 3 ½ months of remaining optimal recruitment time. To put this in perspective, in the last 3 ½ months of this study approximately 110 subjects were randomized. If we enroll the same number during the optimal recruitment period of the enrollment extension, we will have a total enrollment of 240 - 80 subjects short of our goal. These numbers indicate a need to remain focused on recruitment efforts before and after the holiday season.

We expect the holiday season to be challenging in terms of recruitment and enrollment, however, there may be an advantage for many subjects to enroll during this time. If a subject receives pain relief from the study medication, their holidays would be more enjoyable. In addition, subjects should be able to determine whether or not they will tolerate the drug within the first week of therapy. With careful planning of randomization dates, the issue of tolerability is unlikely to interfere with the subjects' holidays.

Please continue to use the upcoming weeks to concentrate your efforts on maximum recruitment and enrollment. Please continue to call us with your enrollment questions. The Analgesia Venture at Abbott Laboratories thanks you for your continuing efforts to make study M99-114 a success.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT241302

Collicott Deposition Exhibit 15

P's Exhibit DB

October 2000
ABT-594 Project Status Report

Monthly Highlights

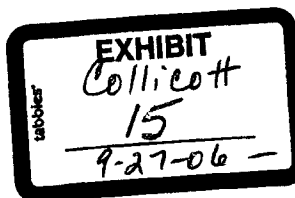
- Options for capsule size, color and design were reviewed with key individuals in PPD and AI. Input from pharmacists on acceptability of options was received. Final decision will be based on meeting both US and international hurdles for color, etc. as well as consideration of ease of identification and handling, and branding.
- Completed Commercial Product Development Continuum Review II
- Completed In-life phase of the mouse carcinogenicity study
- 9 "good will" site visits completed for M99-114

Key Progress Gauges - October Accomplishments	Target Date	Status
• Submit Development Plan for management review	10/05	Complete
• Achieve enrollment of at least 210 patients in M99-114	10/31	Incomplete - 206 patients enrolled as of 10/31
• Complete review of proposals from patient recruitment firms for M99-114 and recommend steps for 1Q01 implementation	10/31	Complete - BBK chosen as best candidate. Working with Abbott Public Affairs and BBK to determine action plan.
• Misunobu impurity profile evaluation (bulk drug substance) to be reviewed with team	10/31	Complete - no unique impurities identified to date

November Projections	Target Date	Status
• Final decision on commercial capsule parameters to be provided by NPD to PARD	11/10	
• Achieve enrollment of at least 220 patients in M99-114 by 11/30	11/30	
• Complete 7 "good will" site visits for M99-114	11/30	
•		

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October 2000
ABT-594 Project Status Report

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture	Extension of enrollment for Phase IIB Neuropathic Pain through 03/01	<ul style="list-style-type: none"> Sites have been notified and contract revisions in process. 2 sites will not participate in extension (Beydoun and Drucker) Budget impact is under evaluation - complete in November.
PARD	During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity was detected in the lot of bulk drug used in M99-114 clinical capsules.	This issue has been reviewed with PARD, Toxicology, Regulatory and Venture Management. To date, the impurity has been detected at a level of 0.2% and efforts are underway to identify. A follow-up meeting is scheduled for November.
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.	PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found. Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision.
NPD	High dropout rate in Phase IIB clinical due to AEs is a significant concern from a commercial perspective if it is indicative of tolerability to be expected in target patient population. Problems with tolerability will be particularly troublesome if pregabalin's tolerability is good; recent pregabalin data in neuropathic pain looks promising with low dropout rate. (APS abstract, Oct 2000)	Recommend continuation of current trial to allow for complete analysis of findings with originally projected power despite delay in timelines. Potential re-positioning of ABT 594 into another market segment, such as opioid-sparing regimens, are under evaluation; this may allow for a commercially viable product.
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long term toxicology studies.	No adenomas have been found in the study. The in-life phase of the 2-year carcinogenicity study is complete and preliminary data on tumor findings should be available 1Q2001.

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October 2000
ABT-594 Project Status Report

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Patent	Follow-on compounds discovered using human recombinant nAChR proprietary technology present increased risk.	<p>Efforts initiated in March, 1999 to negotiate with SIBIA for the rights to use the human recombinant neuronal nicotinic receptor constructs as a screening tool have been terminated due to subsequent exclusive licensing for a period of three years of this technology by SIBIA to Eli Lilly. Merck has subsequently assumed control of SIBIA. To minimize risk associated with the use of the human clonal cell lines, Abbott has initiated a strategy of using only human subtype combinations not currently covered by existing issued US patents. Also, Abbott has initiated a strategy to concurrently pursue the cloning and expression of non-human nAChRs that fall outside the scope of SIBIA's patent estate.</p> <p>Cloning of the ferret $\alpha 4$, $\alpha 3$, $\beta 2$, and $\beta 4$ sub-units is proceeding. Current results suggest that the homology between ferret and human is higher than between rat and human, and is >90% in the highly conserved membrane spanning and ligand binding domains, but that overall homology will likely be less than 90%. It is anticipated that the first of the ferret nAChR subtypes ($\alpha 4\beta 2$) will be completed by 1Q/00.</p> <p>To expand compound libraries and identify novel structural classes, Abbott has partnered with Neurosearch.</p> <p>First joint research council meeting with Neurosearch held 1/31-2/1/00. One compound identified that appears to be 4-fold better based on Chung model vs. emesis model.</p> <p>Evaluating potential anti-depressant compound from this class.</p>

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October 2000
ABT-594 Project Status Report

Project Cost Summary - October					
\$000's Activity	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance
Clinical Program	22.9	6.2	7.1	7.9	.8
CMC (PARD & SPD)	13.0	2.7	3.1	2.6	-5
Drug Safety	8.7	2.6	3.2	2.4	-8
Other Support Costs	0.7	.4	1.0	1.5	.5
Total	50.5	11.9	14.4	14.4	0.0
					215.2

File NDA = 5/2003

Clinical Study Progress				
Protocol # - Study Name	Start (1 st Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients
M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,000	320
				Current Enrollment 206 (as of 10/31)

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Business Rationale

Date: October 2000
Franchise: Neuroscience
Venture: Analgesia

October 2000
ABT-594 Project Status Report

ABT #: ABT-594
Trade & Generic Name: TBD, TBD
Mechanism of Action: Cholinergic Channel Modulator (ChCM)

Indications: Neuropathic Pain
Chronic Pain (publication only)

Product Profile				Market Forecast			
Attribute	Date Defined	Probability*	Confirm Status	Share Impact	PPCC/DOC 12/1996*	Plan as of 6/1996*	Current Revised 10/1996**
Not scheduled	12/1996	High	1Q04	High	Patent Status:	10/2010 (est.)	10/2016 (est.)
Chronic nociceptive pain efficacy	10/1999	Medium	2Q01	High	NDA Filing:	12/1999 (acute)	9/2003
Neuropathic pain claim	6/1999	Medium	2Q01	High	Ex-U.S. Filings:	6/2001 (chronic)	
General pain claim	12/1996	N/A	N/A	High	Same as above - Eur	12/2001 - Eur	9/2003
Moderate to moderately severe pain					N/A - Jpn	12/2003 - Jpn	
No tolerance/dependence or withdrawal	9/1998	Medium	1Q03	High	Projected U.S. Launch:	6/2003	9/2004
Very low abnormal LFTs	9/1998	High	2Q01	High	Projected ex-U.S. Launches:	12/2003 - Eur	Q2 2005 ("average" launch for EU, LA, Canada)
Low nausea/vomiting at effective dose	6/1999	Medium	2Q01	High	Same as above - Eur	9/20/2004 - Jpn	
Other safety OK	9/1998	Medium	2Q01/1Q03	High	N/A - Jpn		Q4 2005 (Average launch for Japan, PAA)
No differential efficacy (nicotine users vs. non users)	9/1998	High	2Q01/1Q03	High	Peak TRx Share, U.S.:	5% (Rx)	20% (Neuropathic pain)
No differential side effect profile (nicotine users vs. non users)	9/1998	Medium	2Q01/1Q03	Medium	6.6% (patients)		10% (Persistent Chronic Pain)
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium	5.4% (patients)	5% (patients)	same as US assumptions
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	Low	4Q01	Medium	Peak TRx Share, ex-U.S.:	\$618	\$367
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium	Peak Sales, U.S.:	\$285	\$466
BID dosing	6/1999	N/A	N/A	Medium	Peak Sales, ex-U.S.:	\$308	\$359
No major drug interactions	12/1996	High	2Q01	High	Pre-Tax NPV @ 15%, ex-U.S.:	\$338	\$296
Titration of 2.5 days duration is required to minimize nausea and vomiting at effective dose.	9/1999	Medium	1Q00	High	After-Tax NPV @ 12.5%, U.S.:	\$412	\$296
					Avg. daily dose	50 mg	150 mcg
					Target Drug Cost/kg at Launch	\$2,500	\$40,000 (base eq.)
					SMM at Launch	94.8%	98.5%
					SMM at Year 5		

* Probability Key:
High > 75%
Medium 50-75%
Low < 50%
N/A Not Applicable

* Forecast based on general peak target indication

** Forecast based on neuropathic pain indication and published study in chronic pain

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October 2000
ABT-594 Project Status Report

Project Overview

Description	Metrics Dates		Activity	Plan 6/1999	Current Revised 6/00	Actual
	Date					
DDC Meeting	12/1996 (PPCC)		Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Start of first GLP animal tox study	2/1997		Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
First dose in human (beg. Phase I)	7/1997		Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
First dose in patient (beg. Phase II)	7/1998		Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
First dose in Phase III	2/2002 (est.)		Phase IIB / Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Last Patient/Last Visit	4/2003 (est.)		Phase IIB Clinical Supplies Manufactured	8/1999	6/2001	TBD
NDA Filing	9/2003 (est.)		NDA Lot (3) Completed	6/2000	12/2001	TBD
NDA Approval	9/2004 (est.)		Completion of 1 Year Stability for NDA	7/2001	2/2003	TBD
Europe (EMEA) Filing	9/2003 (est.)		Formulation Peer Review	10/2001	TBD	TBD
Europe (EMEA) Approval	TBD					
Japan Filing	4/2004 (est.)					
Japan Approval	TBD					

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 6/1999	Actual Date	Plan 6/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	On Test	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	8/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	-	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

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October 2000
ABT-594 Project Status Report

Clinical Study Progress

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Target Cost: \$3 MM

Actual Cost: TBD

Status: Ongoing – 206 patients randomized as of 10/31

Major Findings: TBD

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Marilyn J
Collicott /LAKE/PPRD/ABBO
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To Susan E Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Amy M
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Perri/LAKE/PPRD/ABBOTT, Michael K
Biemesen/LAKE/PPRD/ABBOTT

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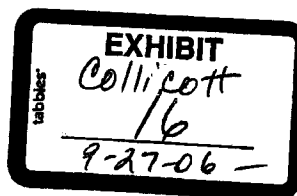
Subject M99-114

Since we don't have a Phase IIB meeting scheduled for this afternoon I'm sending the investigator tracking list that I normally would distribute. It is current as of 10/06/00. Otherwise, there is no new news on either trial.....mc



Investigator tracking.x

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M99-114 INVESTIGATOR LIST

Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened as of 10/06	Total Randomized as of 10/04 11:10	Early Termination 10/06 12:35	as of 10/03 12:13	CRFs in
Backonja	14272	WI	Christy Wessler	(808) 263-0170	1	1			
Baumel (A)	7379	FL	Alfonso Moreno	(305) 865-0063	10	10	4	1	2
Baumel (B)	7379	FL	Jamela Crasto	(561) 368-1123					
Bilon	7396	AR	Donna Hemphill	(501) 227-5061	13	5			
Bromberg	15844	UT	Dallas Forsberg	(801) 585-8051	22	13	4	8	6
DeBolt	15886	MN	Diane Whipple	(952) 993-2739	12	8	2	5	6
Drucker	15843	FL	Ginger Pfaffner	(727) 725-6131	5	4	3		3
Eliaser	15890	FL	Maggie Szymczak	(954) 720-1899	11	1	1		1
Forde (f)	15842	NY	Michael Balotto	(516) 496-6506	2	1	1		1
Fried	12999	RI	Thomas Ricci	(401) 467-7760	14	9	3	4	8
Gibson	15841	AR	Kathy Burke	(501) 227-7499	15	8	3	1	1
Gleason	15840	NM	Mona Chaney	(505) 262-7650	9	7	3	3	7
Haag	15839	MA	Celeste Silva	(413) 794-7232	8	5	4	1	
Hewitt	14345	GA	Ellen McKinzie	(404) 778-3176	6	5	1	1	2
Holmlund	15838	NY	Marie Caserta	(716) 887-4793	11	5	3	2	
Kalka - A	12497	PA	Donna Cole	(814) 693-0300	12	5	1		
Kalka - B	12497	PA	Sherry Minor	(814) 943-3668					
Kipnes	15062	TX	Lisa Unde	(210) 615-5565	21	15	5	6	4
Kirby	9576	AZ	Stephanie Marshall	(623) 815-9714	13	6	1		2
Klupe (f)	13435	FL	Joann Stratton	(941) 938-4421	21	8	2	3	5
McGill (f)	15837	MO	Katherine Anderson	(314) 362-1404	16	8	1	2	
Rowbotham	14348	CA	Jessica McCoy	(415) 885-7899	12	3	1	2	3
Shabani	16334	TX	George Manoukian	(713) 795-0033	16	5			
Simmons	15836	PA	Kathleen Hay	(717) 531-8694	4	3	2		1
Singer	16230	FL	Marcy Novaro	(954) 433-5785	16	10	4		
Sivakumar	15833	AZ	Sandra Somers	(602) 287-8026	11	7	2	4	4
Steel	15923	NC	Margo Stock	(252) 752-4848	9	8	6	2	2
Storey	14349	NY	Paula Levin	(516) 438-0922	17	9	3	1	3
Suri	15269	CA	Kuldip Thussu	(559) 595-1861	4	3			
Vinik	15834	VA	Polly Morgan	(757) 446-5912	14	6			
Weinstein	13033	CA	Julie Vigil	(925) 930-7267	21	8	4	2	3
					346	185	64	46	64

Screen Failure Rate: 53%
 Early Termination Rate: 35%
 Completion Rate: 26%

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Screen Tracking

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M88-114 Early Terminations

Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Barnes	4145	83	1	AE	nausea, etc.
	4146	76	10	AE	dizziness, weakness, heart palpitations, headache, blurred vision
	4147	85	11	AE	dizziness, weakness, swelling, blurred vision, heartburn, headache
	4113	89	10	AE	nausea, etc.
Bromberg	4115	45	5	AE	nausea, etc.
	4117	50	7	AE	nausea, etc.
	4118	50	7	AE	dizziness, vomiting, nausea
	4051	71	9	AE	nausea, etc.
Deloid	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	int. nausea/vomit since 5/1, int. food bloating & constipation, dark urine stream since 8/26
	4001	72	3.5	AE	left pain in lower extremities
	4002	71	3	SAE	palpitations
Eltner	4003	78	0.5	AE	blurred vision
	4241	80	1	AE	nausea, etc. (went to ER)
	4321	87	5	AE	dizziness, drowsiness
	4083	85	14	SAE	apical episode related to hypertensive crisis (went to hospital 5/20)
Fried	4087	74	4	AE	dizziness, GI upset, fatigue, light-headedness (patient took every dose following a meal)
	4354	73	1.5	AE	nausea
	4164	51	1	AE	dizziness, disorientation
	4185	51	1	AE	dizziness, disorientation
Hagg	4187	70	7	AE	dizziness - 2hrs post-dose x 10 episodes
	4337	43	5.5	AE	difficulty falling asleep, awakening more frequently
	4340	72	5	AE	nausea, etc.
	4193	53	7	AE/SAE	vomiting, fatigue, broken pills
Hornlund	4185	50	7	AE	nausea, vomiting
	4187	52	4	SAE	chest pain
	4417	74	6	AE	nausea, vomiting
	4049	64	7	AE	low pain, insomnia, increased BP, heart palpitations, fatigue
Koslos	4055	64	3.5	AE	nausea
	4066	55	25	AE	nausea
	4070	48	10	SAE	leg arm pain
	4072	70	7	AE	nausea, etc.
Kufly	4075	74	2	AE	nausea, etc.
	4178	82	9	AE	nausea, etc.
	4131	70	8.5	AE	nausea, etc.
	4133	66	5.5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 5/6-8/10)
McGill	4337	85	7	AE	nightmares, insomnia, nausea
	4273	58	11	AE	GI ex. cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	69	10	AE	vomiting, nausea, headache, viral disease, dizziness, chills
	4403	57	10	AE	vomiting
Shelton	4408	68	6	AE	vomiting
	4036	58	2.5	AE	nausea, etc.
	4038	50	2.5	AE	nausea, etc.
	4209	68	22	AE	light-headed, dizzy
Steel	4210	73	9	AE	vomiting
	4215	60	10	AE	nausea
	4216	62	10	AE	nausea
	4098	70	6.5	AE	nausea, etc.
Storoy	4100	56	3	AE	nausea, etc.
	4102	69	3	AE	nausea, etc.
	4020	73	3	AE	nausea, etc.
	4021	65	13	AE	coughs, sore throat, cold (went to ER)
Wainstein	4024	63	13	AE	coughs, sore throat, cold (went to ER)
	4024	63	13	AE	coughs, sore throat, cold (went to ER)
	4024	63	13	AE	coughs, sore throat, cold (went to ER)
	4024	63	13	AE	coughs, sore throat, cold (went to ER)

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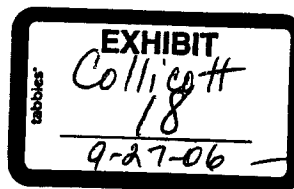
ABT-594

Descriptive Memorandum

November 2000

Abbott Laboratories

Highly Confidential



ABBT144600.UR

ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release). Peak sales of ABT-594 are projected to reach over \$420MM in the US and \$362MM ex-US by 2008.

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth. Of even greater impact on total market sales, most of the agents used to treat this population, with this exception of Neurontin, are low-cost, generic products.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
TOTAL	\$351	21.7%	\$140	10.1%
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

Competition, Products in Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through $\alpha 2$ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

Analgesia Development Pipeline -- Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Predclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Predclinical	Target is pain
FID 072021	Fidia	Predclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Predclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimocromol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

Product / Development Background

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients are anticipated to be included in the study.

Patent Status

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing composition of matter coverage for a large class of structurally related neuronal nicotinic receptor analogs, which encompasses ABT-594 (5246.U.S.) The original filing date for this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 under this patent is June 2016.

An additional application (6013.US.01) which includes a use claim for ABT-594 species in analgesia was filed in September 1997, with subsequent divisional filing of ABT-594 species composition of matter. Despite this later composition of matter filing for the species claim, it is likely that a "terminal disclaimer" will be necessary that dates the composition of matter claim back to the original genus patent (5246.U.S.) We have paid the issue fee for this patent on July 19, 2000, and are anticipating the patent to issue 90 - 120 days from that date. If this patent is allowed, it will provide 20 years from date of filing for the use of ABT-594 in analgesia, which will extend the patent life of ABT-594 to September 2017.

The original application providing generic composition of matter coverage was filed broadly ex-U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

As additional information regarding potential uses for ABT 594 is gathered, applications to expand the scope of ABT 594's patent will be submitted. A task force consisting of members of NUDR, the Analgesia Venture, New Product Development, the Neuroscience Franchise, and the Abbott Patent Department will conduct periodic review of the patent.

Considerations

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug Interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
 - 2) Treatment of post-herpetic neuralgia
 - 3) Treatment of neuropathic pain
 - 4) Treatment of chronic pain
 - 5) Treatment of cancer pain

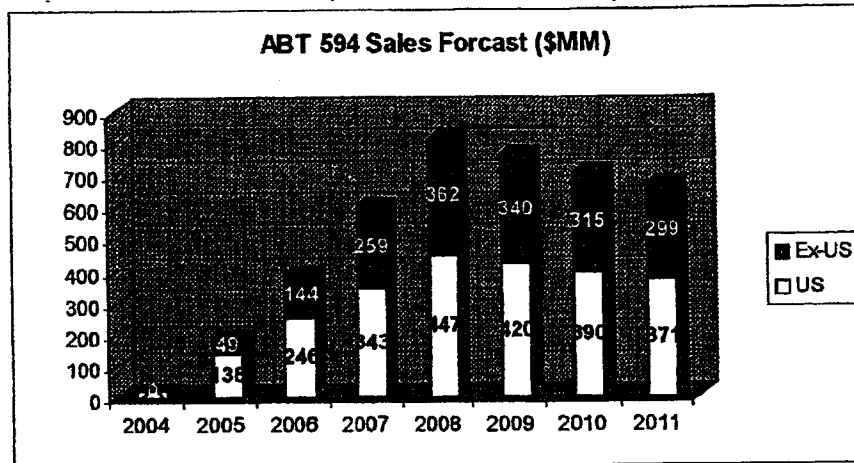
Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

Financial Projections**Key US forecast assumptions:**

- First neuronal nicotinic receptor compound for pain to market
- Indicated for treatment of neuropathic pain; significant publication, or indication, from large scale trial on use in some form of chronic persistent nociceptive pain (e.g., OA) in 2006
- Efficacy greater than gabapentin in neuropathic pain and COX-2s in chronic nociceptive pain
- Good safety profile (no significant warnings or contraindications)
- Tolerability profile in line with other chronic pain products (CNS side effects improved over Neurontin and GI side effects improved over tramadol)
- No addictive potential
- Titration of 3-5 days
- Peak share 20% in neuropathic pain, 10% in chronic, persistent nociceptive pain (including off-label, 'spillover' prescriptions)
- Significant promotional and PR spend in early years
- Physician targets: D6-10 Neurologists, D3-10 Rheumatologists/Endocrinologists, D9-10 PCPs
- Sampling at 80% of details at launch, 5 units per detail, 7 days of therapy per unit
- Cost comparable to Neurontin and Celebrex
- Significant payor discounting
- Stocking at 8% of first year's sales
- Patent expires 12/2016

Additional Ex-US forecast assumptions:

- Same profile and peak share assumptions as U.S. forecast
- Price (ASP) = \$0.90 per day, or \$27 per 30 day Rx (comparable to COX-2 pricing)
- Average AI launch assumption is Q1 2005 to allow for additional regulatory filings (COFS and national filings in PAA and LA) and/or pricing negotiations (most markets in Europe) required in AI markets

Collicott Deposition Exhibit 22

P's Exhibit DU

December 2000
ABT-594 Project Status Report

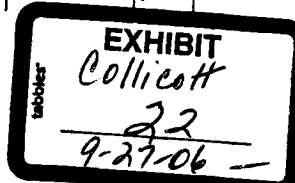
Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture	Closing of enrollment on M99-114 as of January 5, 2001	<ul style="list-style-type: none"> Enrollment will be closed on this revised date. Timeline impact will be reviewed in January
PARD	During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study	<p>This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made.</p> <ul style="list-style-type: none"> Due to significant chemistry challenges, the delivery of impurity F' to PARD from SPD is delayed. New target date to be determined pending favorable results from current synthesis efforts. PARD Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot; planned January 2001 When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.	PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found.
NPD	Portfolio analysis process is underway for ABT 594 and will impact budget allocation for 2001. A new forecast using updated NPD forecast model with clearly defined product profile and high and low case estimates is being developed and will be reviewed by core team prior to final conduct of portfolio prioritization.	Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision. ABT 594 portfolio team reviewed the forecasts and profile on 12/19/00. Final adjustments are in process, and will be completed no later than 1/15/01 (just prior to prioritization meeting).
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long-term toxicology studies.	No adenomas have been found in the study. The in-life phase of the 2-year carcinogenicity study is complete and preliminary data on tumor findings should be available 1Q2001.

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December 2000
ABT-594 Project Status Report

Project Cost Summary - November						
\$000's Activity	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	22.9	7.5	7.5	7.9	.4	157.1
CMC (PARD & SPD)	13.0	2.9	2.9	2.6	-.3	27.6
Drug Safety	8.7	3.4	3.4	2.4	-1.0	18.3
Other Support Costs	0.7	.5	.5	1.5	1.0	12.2
Total	50.5	14.3	14.3	14.4	.1	215.2

File NDA = 9/2003

Clinical Study Progress				
Protocol # - Study Name	Start (1st Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients
M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,000	320
				Current Enrollment 267 (As of 12/31)

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December 2000 ABT-594 Project Status Report

Business Rationale

Date: November 2000
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594
Trade & Generic Name: TBD, ebanciline tosylate
Mechanism of Action: Neuronal Nicotinic Receptor (NNR) Agonist

Indications: Neuropathic Pain
Chronic Pain (publication only)

Product Profile				Market Forecast			
Attribute	Date Defined	Probability*	Confirm Status	Share Impact	PPCC/DOC 12/1998*	Plan as of 6/1998*	Current Revised 1/2001**
Not scheduled	12/1996	High	1004	High	Patent Status: 10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
Chronic nociceptive pain efficacy	10/1999	Medium	2001	High	NDA Filing: 12/1999 (acute)	12/2001	9/2003
Neuropathic pain claim	6/1999	Medium	2001	High	6/2001 (chronic)	12/2001 - Eur	9/2003
General pain claim	12/1996	N/A	N/A	High	Same as above - Eur	12/2003 - Jpn	
Moderate to moderately severe pain					N/A - Jpn		
No tolerance/dependence or withdrawal	9/1998	Medium	1003	High	Projected U.S. Launch: 12/2001 (acute)	6/2003	9/2004
Very few abnormal LFTs	9/1998	High	2001	High	12/2002 (chronic)		
Low nausea/vomiting at effective dose	6/1999	Medium	2001	High	Projected ex-U.S. Launches: Same as above - Eur	12/2003 - Eur	Q2 2005 ("average" launch for EU, LA, Canada)
Other safety OK	9/1998	Medium	2001/1003	High	N/A - Jpn	9/20/2004 - Jpn	
No differential efficacy (nicotinic users vs. non users)	9/1998	High	2001/1003	High			Q4 2005 (Average launch for Japan, PAA)
No differential side effect profile (nicotinic users vs. non users)	9/1998	Medium	2001/1003	Medium	Peak TRx Share, U.S.: 6.6% (patients)	5% (Rx)	20% (Neuropathic pain)
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium			5% (Persistent Chronic Pain)
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	Low	4001	Medium	Peak TRx Share, ex-U.S.: 5.4% (patients)	5% (patients)	same as US assumptions
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium	Peak Sales, U.S.: (\$MM)	\$285	\$339
BID dosing	6/1999	High	2001	High	Peak Sales, ex-U.S.: (\$MM)	\$308	\$466
No major drug interactions	12/1996	High	1003	Medium	Pre-Tax NPV @ 12.5%, ex-U.S.: (\$MM)	\$338	\$535
Titration of 2-5 days duration is required to minimize nausea and vomiting at effective dose.	9/1999	Medium	1000	High	After-Tax NPV @ 12.5%, U.S.: (\$MM)	\$813	\$316
					Avg. daily dose	200 mcg	150 mcg
					Target Drug Cost/kg at Launch	\$2,500	\$40,000 (base eq.)
					SMM at Launch (US)	97.2%	91.6%
					SMM at Year 5 (US)		92.2%

Probability Key:

* Probability Key:
High = 70-100%
Medium = 30-69%
Low = 0-29%

** Forecast based on general pain target indication
** Forecast based on neuropathic pain indication and published study in chronic pain

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December 2000
ABT-594 Project Status Report

Project Overview

Metrics Dates		PARD	
Description	Date	Plan	Current Revised
DOC Meeting	12/1996 (PPCC)	6/1999	10/00
Start of first GLP animal tox study	2/1997	7/1997	7/1997
First dose in human (beg. Phase I)	7/1997	7/1998	7/1998
First dose in patient (beg. Phase II)	7/1998	7/1998	7/1998
First dose in Phase III	2/2002 (est.)	10/1998	10/1998
Last Patient Last Visit	4/2003 (est.)		
NDA Filing	9/2003 (est.)	3/1999	3/1999
NDA Approval	9/2004 (est.)	9/1999	9/2001
Europe (EMEA) Filing	9/2003 (est.)	6/2000	5/2002
Europe (EMEA) Approval	TBD	7/2001	7/2003
Japan Filing	4/2004 (est.)	10/2001	TBD
Japan Approval	TBD		

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 6/1999	Actual Date	Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	On Test	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

Toxicology		Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology		2/1997	9/1996	8/1997
Acute Studies		3/1997	4/1997	8/1997
1 Month Rat/Monkey		2/1997	2/1997	11/1997
3 Month Rat/Monkey		7/1997	6/1997	8/1998
3 Month Mouse MTD		10/1997	6/1997	10/1998
SEG I and SEG II		10/1997	7/1997	7/1998
SEG III Rat (post natal development)		-	1/1999	Ongoing
6 Month Rat		1/1998	3/1998	7/1999
1 Year Monkey		6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat		12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse		12/1998	11/1998	Ongoing

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December 2000
ABT-594 Project Status Report

Clinical Study Progress

<p>Protocol:</p> <p>Objective:</p> <p>ABT-594 Doses:</p> <p>Comparator Doses:</p> <p>Target Enrollment:</p> <p>Target Cost:</p> <p>Actual Cost:</p> <p>Status:</p> <p>Major Findings:</p>	<p>M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy</p> <p>The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.</p> <p>150 µg, 225 µg, and 300 µg twice daily (BID)</p> <p>Placebo</p> <p>320</p> <p>\$3 MM</p> <p>TBD</p> <p>Ongoing – 267 patients randomized as of 12/31</p> <p>TBD</p>
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D:\77\LMPSR\Nov. 2000\ABT-594 November 2000 MPSR.doc

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Collicott Deposition Exhibit 23

P's Exhibit IH

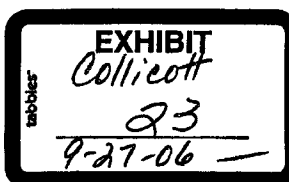
December 2000 - "Top" Issues

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Redacted		
ABT-492 Clinical	Phase I single rising dose was completed 12/15/00.	Doses ranging from 50 mg to 1600 mg were administered with no serious adverse events. Urine samples indicate that the drug is available in the urine and that UTI indications can be pursued.
ABT-594	Closing of enrollment on M99-114 as of January 5, 2001	It was agreed in December to close enrollment into M99-114, our Painful Diabetic Neuropathy trial, as of January 5, 2001. This is 2 months ahead of our most recent estimate of March 5, 2001, and will include less than our original target of 320 patients. The acceleration of the study close date was driven by our desire to evaluate the outcome of the study, and an assessment of the statistical power of the study.
ABT-627 NPD	During investigative work on implementation of the Milanobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, In vitro micronucleus assay and bioavailability study	<ul style="list-style-type: none"> This issue has been reviewed with PARC, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made. Due to significant chemistry challenges, the delivery of impurity F' to PARC from SPD is delayed. New target date to be determined pending favorable results from current synthesis efforts. PARC Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot; planned January 2001 <p>When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics</p>
ABT-731 PARC	Submitted on 12/1 six abstracts for Spring AUA and ASCO annual meetings.	
ABT-773 NPD	Development of final formulation for Phase I studies completed 12/31.	
	Phase IIIa data will be important predictors of commercial value	Phase IIIa studies to be complete 5/2001. FDA changes to the Phase III protocols creates a

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ABBT0017554



Collicott Deposition Exhibit 24

P's Exhibit DV



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT

12/06/2000 02:04 PM

To: Michael K Biamesen/LAKE/PPRD/ABBOTT
cc:
bcc:
Subject: Re: November Monthly Project Status Report, ABT-594 []

Wellllllllllllllllllll - OK. I just have a feeling the bottom is going to drop out of this thing in the next few weeks and we'll be lucky to randomize 1-2/week. (Oh God - I'm turning into an Eeyore!!)
Michael K Biamesen

Michael K Biamesen

12/06/2000 01:07 PM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: November Monthly Project Status Report, ABT-594 []

How about 260 for the randomization goal? We already have 251 !!!!!.
Marilyn J Collicott



Marilyn J Collicott

12/04/2000 02:13 PM

To: Michael K Biamesen/LAKE/PPRD/ABBOTT
cc:
Subject: Re: November Monthly Project Status Report, ABT-594 []

Mike

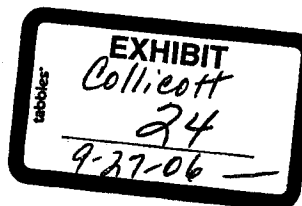
Monthly Highlights:

Reviewed proposals and timelines from 3 subject recruitment firms. Determined that hiring a subject recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.

December Projections:

254 subjects randomized for study M99-114.

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ABBT242373

Draft

Name: Christopher Elmer, M.D.
Title: Head, Analgesia VentureDIVISION INCENTIVE PLAN GOALS
2001 DIP

Manager: John Leonard

Any approved division incentive plan "DIP" award will be dependent upon division results and individual performance against impact goals and leadership competencies as evaluated by the senior vice president ("President"). Each impact goal category must have a minimum of one (1) goal and no more than eight (8) goals across all three (3) categories. Impact goal weight minimum is 5%.

Leadership Competencies	Weighting %	Competency Performance
1. Set Vision and Strategy 2. Build Organization and Inspire People 3. Know the Business 4. Drive Results 5. Make Difficult Decisions 6. Encourage an Open Environment and Knowledge Sharing	20	

Impact Goal Categories	Goal and Expected Result	Results Achieved	Weighting %	Goal Performance
Financial	1. Operate within Plan Head Count of XX and Expenses of \$XXXX, or as modified in Updates or Blue Prints (2000 = XXXXX).	1.	15	
Business Process	2. Execute sufficient data for ABT-594 GONNO GO decision by 2Q 01. • Last patient enrolled in Phase 2 Neuropathic Pain Study 301.	2.	15	
	3. If GO decision for ABT-594, complete preparation for 1Q 02 initiation of Phase 3. • Manufacture bulk drug substance by 3Q 01 to support Phase 3 clinical supplies. • Manufacture clinical supplies by 4Q 01 to support initiation of Phase 3. • End of Phase 2 (or equivalent) meetings with regulatory authorities by 12/01. • Protocol approval for all planned pivotal studies by 1Q 02.	3.	10	
	4. Achieve ABT-594 transition team GONNO GO decision by 4Q 01. • Initiate first-time-in-man study by 4Q 01. • Complete dosage form assessment (sustained-release form viability) by 11/01.	4.	15	
	5. Working with Neuroscience Franchise team, in-license one compound and recommend strategy for company acquisition or alliance by 12/01.	5.	10	
	6. Demarcate Neuroscience Franchise transition team strategy by 2Q 01.	6.	5	
People Management	7. Achieve priority people initiatives. • Ensure Performance Excellence program initiatives are met by year end.	7.	5	
	8. Retain 80% of the "O" performers and identified high potentials.	8.	5	
TOTAL GOAL PERFORMANCE			100	

12/01/00

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ABBT242394

Collicott Deposition Exhibit 25

P's Exhibit DX



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
12/14/2000 03:43 PM

To Marian L Borgstrom/LAKE/PPRD/ABBOTT@ABBOTT, Lila J
Davis/LAKE/PPRD/ABBOTT, Carol J
Feige/LAKE/PPRD/ABBOTT@ABBOTT, Catherine K
Kacos/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T
Matalonis/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Raymond A
Morales/LAKE/PPRD/ABBOTT@ABBOTT, Nancy M
Palbicke/LAKE/PPRD/ABBOTT@ABBOTT, Joan M
Perr/LAKE/PPRD/ABBOTT, Christopher J
Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Biamesen/LAKE/PPRD/ABBOTT, Judith A
Sweetwood/LAKE/PPRD/ABBOTT@ABBOTT, David C
Ross/LAKE/PPRD/ABBOTT@ABBOTT, James W
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, David D
Morris/LAKE/PPRD/ABBOTT@ABBOTT, Judith S
Brownell/LAKE/PPRD/ABBOTT@ABBOTT, Susan E
Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Linda M
Fisher/LAKE/PPRD/ABBOTT@ABBOTT, Tamara L
Garavalia/LAKE/PPRD/ABBOTT@ABBOTT, Beth H
Wilson/LAKE/PPRD/ABBOTT, Walid
Awni/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep
Dutta/LAKE/PPRD/ABBOTT@ABBOTT, Teresita P
Curry/LAKE/PPRD/ABBOTT@ABBOTT, Barbara T
Messa/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

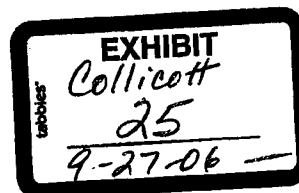
Subject Study M99-114

A decision has been made to stop enrollment for study M99-114 on January 5, 01. Subjects may be randomized up through that date. I've attached a copy of the letter that is being FedExed to all sites today. If you have any questions, please don't hesitate to contact me..... mc



stopenroll

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ABBT236951

December 14, 2000

<name>
<address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. <name>,

We have decided to end enrollment in the above referenced study on January 5, 2001.

As specified in the protocol, 80% power would have been achieved with the randomization of 320 subjects, assuming there were no premature terminations. Our current premature termination rate, however, will result in less than 80% power even if we were to reach our enrollment goal. After reviewing possible outcomes with our statisticians, we concluded that ending enrollment prior to reaching our goal of 320 subjects will not meaningfully change our ability to interpret the results of this study. In addition, the sooner we review the data from M99-114, the sooner we may be able to move forward into Phase III.

In order to allow you to enroll any subjects that may have already been scheduled, the last date for randomization into study M99-114 will be 1/5/01. We sincerely apologize if this causes you or your staff any inconvenience.

The Analgesia Venture thanks you for your hard work and dedication to ABT-594 and study M99-114. Your efforts have allowed us to move forward more quickly than anticipated. If you have any questions or concerns please don't hesitate to contact me.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT236952

Collicott Deposition Exhibit 26

P's Exhibit 20



Marilyn J
Collicott/LAKE/PPRD/ABBO
TT
12/14/2000 12:20 PM

To JSCHANZENBACH@rsi-nc.com@internet
cc
bcc
Subject Study Termination

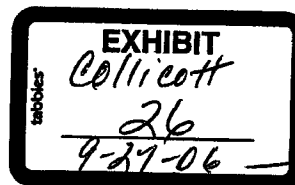
Hi John

We've decided to end enrollment as of 1/5/01. The attached letter (which explains our reasoning) will be fedexed out to all investigators today. You may get some phone calls tomorrow. Let me know if you have any questions. Thanks.....mc



stopenroll

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ABBT233539

December 14, 2000

<name>
<address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. <name>,

We have decided to end enrollment in the above referenced study on January 5, 2001.

As specified in the protocol, 80% power would have been achieved with the randomization of 320 subjects, assuming there were no premature terminations. Our current premature termination rate, however, will result in less than 80% power even if we were to reach our enrollment goal. After reviewing possible outcomes with our statisticians, we concluded that ending enrollment prior to reaching our goal of 320 subjects will not meaningfully change our ability to interpret the results of this study. In addition, the sooner we review the data from M99-114, the sooner we may be able to move forward into Phase III.

In order to allow you to enroll any subjects that may have already been scheduled, the last date for randomization into study M99-114 will be 1/5/01. We sincerely apologize if this causes you or your staff any inconvenience.

The Analgesia Venture thanks you for your hard work and dedication to ABT-594 and study M99-114. Your efforts have allowed us to move forward more quickly than anticipated. If you have any questions or concerns please don't hesitate to contact me.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT233540

Collicott Deposition Exhibit 27

P's Exhibit ED

January 2001
ABT-594 Project Status Report

Monthly Highlights

Enrollment closed for our Phase IIb Painful Diabetic Polyneuropathy trial (M99-114), with total enrollment reaching 269. The last patient will complete the study at the end of February, and results will be available at the end of May.

Key Progress Gauges - January Accomplishments	Target Date	Status
• Close enrollment into M99-114	01/05	Complete
• Portfolio analysis team analyses submitted to Chris Turner	01/15	Complete
• Prepare study close-out timelines	01/22	Complete
• Complete preparations for February 2 Project Review with Jeff Leiden and Senior Management	01/31	Complete

February Projections	Target Date	Status
• Project Review with Jeff Leiden and Senior Management	02/02	
• 250 completed Case Books in-house for M99-114	02/28	



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**January 2001
ABT-594 Project Status Report**

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture	Closed enrollment on M99-114 on January 5, 2001	<ul style="list-style-type: none"> Complete
PARD	<p>During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study</p>	<p>This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made.</p> <ul style="list-style-type: none"> Due to significant chemistry challenges, the delivery of impurity F' to PARD from SPD is delayed. New target date to be determined pending favorable results from current synthesis efforts. PARD Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot. When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.	<p>PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found.</p> <p>Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision.</p>
NPD	<p>Portfolio analysis to be reviewed by Senior Management on January 29.</p> <p>Project review presentation to Jeff Leiden scheduled for February 2.</p>	<p>Portfolio analysis process is complete and forecasts have been updated. Base case forecast now reflects value of neuropathic pain indication only (publication in chronic nociceptive pain is considered upside, and a separate funding issue). Commercial presentation to Jeff Leiden complete.</p>
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long-term toxicology studies.	<p>No adenomas have been found in the study. The in-life phase of the 2-year carcinogenicity study is complete and preliminary data on tumor findings should be available 1Q2001.</p>

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January 2001
ABT-594 Project Status Report

Project Cost Summary - November

\$000's Activity	Cumulative through 2000	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	34.8	0.8	6.2	6.2	...	150.9
CMC (PARC & SPD)	16.3	0.2	1.0	1.0	...	26.6
Drug Safety	11.6	0.1	1.4	1.4	...	16.9
Other Support Costs	2.1	...	0.7	0.7	...	11.5
Total	64.8	1.1	9.3	9.3	...	205.9

File NDA = 9/2003

Clinical Study Progress

Protocol # - Study Name	Start (1 st Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients	Current Enrollment
M99-114 - A Randomized, Double-Blind, Placebo- Controlled Comparison of the Safety and Efficacy of ABT- 594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,100	320	269 (Final)

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January 2001 ABT-594 Project Status Report

Business Rationale

Date: January 2001
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594
Trade & Generic Name: TBD, ebanicline tosylate
Mechanism of Action: Neuronal Nicotinic Receptor (NNR) Agonist

Indications: Neuropathic Pain

Product Profile

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Not scheduled	12/1996	High	1Q04	High
Chronic nociceptive pain efficacy	10/1999	N/A	N/A	High
Neuropathic pain claim	6/1999	Medium	2Q01	High
General pain claim	12/1996	N/A	N/A	High
Moderate to moderately severe pain	9/1998	Medium	1Q03	High
No tolerance/dependence or withdrawal	9/1998	High	2Q01	High
Very low abnormal LFTs	6/1999	Medium	2Q01	High
Low nausea/vomiting at effective dose	9/1998	Medium	2Q01/1Q03	High
Other safety OK	9/1998	High	2Q01/1Q03	High
No differential efficacy (nicotine users vs. non users)	9/1998	Medium	2Q01/1Q03	Medium
No differential side effect profile (nicotine users vs. non users)	9/1998	N/A	N/A	Medium
No reinitiation of cravings in ex-nicotine users	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	High	2Q01	High
BID dosing	12/1996	High	1Q03	Medium
No major drug interactions	9/1999	Medium	1Q00	High
Titration of 2-5 days duration is required to minimize nausea and vomiting at effective dose.				

* Probability Key:
High = 70-100%
Medium = 30-69%
Low = 0-29%

Market Forecast

PPCC/DDC 12/1996*	Plan as of 6/1996*	Current Revised 12/2001**
10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
12/1999 (acute)	12/2001	9/2003
6/2001 (chronic)	12/2001 - Eur	9/2003
Same as above - Eur	12/2003 - Jpn	
N/A - Jpn	6/2003	9/2004
12/2001 (acute)		
12/2002 (chronic)	12/2003 - Eur	Q2 2005 (Average* launch for EU, LA, Canada)
Same as above - Eur	9/20/2004 - Jpn	Q4 2005 (Average launch for Japan, PAA)
N/A - Jpn		20% (Neuropathic pain)
6.6% (patients)	5% (Rx)	5%
Peak TRx Share, U.S.:		(Persistent Chronic Pain) same as US assumptions
Peak TRx Share, ex-U.S.:	5% (patients)	\$339
Peak Sales, U.S.:	\$285	\$363
Peak Sales, ex-U.S.:	\$308	\$356
Pre-Tax NPV @ 12.5%, ex-U.S.:	\$338	\$313
After-Tax NPV @ 12.5%, U.S.:	\$412	150 mcg
Avg. daily dose	50 mg	\$40,000 (base eq.)
Target Drug Cost/kg at Launch	\$2,500	91.6%
SMM at Launch (US)	94.8%	92.2%
SMM at Year 5 (US)		

* Forecast based on general pain target indication

** Forecast based on neuropathic pain indication (diabetic polyneuropathy)

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January 2001
ABT-594 Project Status Report

Project Overview

Metrics Dates	
Description	Date
DDC Meeting	12/1996 (PPCC)
Start of first GLP animal tox study	2/1997
First dose in human (beg. Phase I)	7/1997
First dose in patient (beg. Phase II)	7/1998
First dose in Phase III	2/2002 (est.)
Last Patient/Last Visit	4/2003 (est.)
NDA Filing	9/2003 (est.)
NDA Approval	9/2004 (est.)
Europe (EMEA) Filing	9/2003 (est.)
Europe (EMEA) Approval	TBD
Japan Filing	4/2004 (est.)
Japan Approval	TBD

PARD

Activity	Plan 8/1999	Current Revised 10/00	Actual
Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped	10/1998	10/1998	10/1998
(Osteoarthritis, Surgery, Neuropathy)			
Phase IIB / Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lots (3) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 8/1999	Actual Date Received	Plan 8/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	2/2001 **	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	2/2001 **	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	2/2001 **	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

** Bulk manufactured 1/2000, but delivery delayed due to Mesylate testing & QA release

Toxicology

Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	8/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	-	1/1998	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

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January 2001
ABT-594 Project Status Report

Clinical Study Progress

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Target Cost: \$3 MM

Actual Cost: TBD

Status: Enrollment Complete – 269 patients randomized

Major Findings: TBD

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D's Exhibit LI


 Marilyn J Collicott / LAKE / PPRD / ABBOTT
 TT
 01/08/2001 02:35 PM

To JSCHANZENBACH@rsi-nc.com@internet
 cc
 bcc
 Subject M99-114 crf tracking, 08/JAN/01

FYI - query tracking report. This becomes quite the big deal at this stage of the game..... mc
 Forwarded by Marilyn J Collicott/LAKE/PPRD/ABBOTT on 01/08/2001 02:34 PM


 Judith S Brownell
 01/08/2001 12:26 PM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT
 cc: Katherine M Landwer/LAKE/PPRD/ABBOTT@ABBOTT, Brenda Martino/LAKE/PPRD/ABBOTT@ABBOTT, Susan E Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Beth H Wilson/LAKE/PPRD/ABBOTT@ABBOTT
 Subject: M99-114 crf tracking, 08/JAN/01

ABT-594 TRACKING REPORT AS OF 08/JAN/01

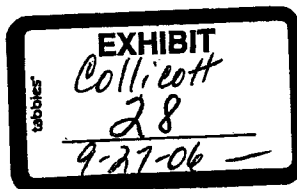
Study #/ # subjects expected (n=x)	Study Coordinator/ extension #	Subjects enrolled to date	Subjects received in D433 separation to date	Entered and verified to date	Estimated % of expected crf pages received to date	Mean QA Time (days)*	Subjects clean to date**	Subjects with unresolved queries to date	Unresolvd DM queries to date
M99-114	Judy Brownell 7-3840	269	141	141	62	2.0	0	96	248

*Median QA time is 2.0, mean QA time is 5.1 due to delay beginning of study implementation of CDC QA Plan.

**Cannot be determined until all CRF's received

jb

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P's Exhibit SK



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT

01/16/2001 11:29 AM

To JSCHANZENBACH@rsi-nc.com@internet
cc
bcc
Subject Meeting Today

John

Here are copies of the agenda and handouts for today's meeting..... mc



agenda.doc



Investigator tracking.xls

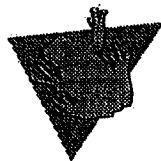


Subject-CRF Tracking.xls

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AGENDA
M99- 114
Phase II B Meeting
1/16/01
3:00 - 4:00

- 114 Update Marilyn
 - ⇒ final enrollment
 - ⇒ CRF retrieval
 - ⇒ query resolution
- Data Management Judy/ Katie
- Statistics Jim
- Drug Forms Carol
- Tracking Joan
- Payments Ray/ Jan
- Discussion All

Notes:

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ABBT242694

M99-114 INVESTIGATOR LIST

Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened	Total Terminated	Total Completed	Total Incomplete	Total Incomplete %	Total Incomplete %
Backus	14272	WI	Cheryl Wheeler	(808) 269-0170	4	0	0	0	0	0
Baumel (A)	7379	FL	Alonso Moreno	(305) 865-0063	28	15	13	15	53.6%	7
Baumel (B)	7379	FL	Jessie Costa	(561) 368-1123	28	15	13	15	53.6%	7
Bison	7398	AR	Doreen Verrill	(501) 227-5081	28	18	10	18	64.3%	8
Bromberg	15844	UT	Doreen Baum	(801) 545-5051	28	25	3	25	89.3%	3
DeBolt	15808	MI	Dore Whipple	(952) 993-2738	28	17	11	17	60.7%	11
Drucker	15843	FL	Ginger Peltier	(727) 725-6131	28	7	21	7	25.0%	21
Elmer	15890	FL	Maggie Bzymczak	(854) 720-1899	28	12	16	12	42.9%	16
Forde (I)	15842	NY	Michael Boates	(516) 496-8506	28	5	23	5	17.9%	23
Fried	12909	RI	Thomas Hoot	(401) 487-7780	28	19	9	19	67.9%	9
Gibson	15841	AR	Kathy Burke	(501) 227-7469	28	28	0	28	100.0%	0
Glesson	15840	NM	Mona Chaney	(505) 262-7650	28	28	0	28	100.0%	0
Heag	15838	MA	Conner Sims	(413) 794-7232	28	28	0	28	100.0%	0
Hewitt	14345	GA	Elan McKee	(404) 778-3176	28	28	0	28	100.0%	0
Holmblad	15835	NY	Mina Kassam	(718) 867-4793	28	1	27	1	3.6%	27
Kafka - A	12497	PA	Doreen Cole	(614) 893-0300	28	18	10	18	64.3%	10
Kafka - B	12497	PA	Sherry Mince	(614) 843-3668	28	18	10	18	64.3%	10
Kirwan	15062	TX	Lisa Little	(214) 815-5565	28	28	0	28	100.0%	0
Kirby	9578	AZ	Stephanie Marshall Kate Marshall	(602) 815-8714	28	20	8	20	71.4%	8
Klyne (I)	15435	FL	Monique Wolf	(941) 835-4421	28	24	4	24	85.7%	4
McGill (I)	15837	MO	Katherine Anderson	(314) 382-1404	28	17	11	17	60.7%	11
Rowbottom	14348	CA	Jessie McCoy	(415) 885-7999	28	13	15	13	46.4%	15
Shabert	16334	TX	George Mercusian	(713) 795-0033	28	48	18	48	171.4%	18
Simmons	15236	PA	Kathleen Hay	(717) 531-8904	28	7	21	7	25.0%	21
Singer	18230	FL	Mary Newco	(954) 439-5785	28	30	15	30	107.1%	15
Sivakumar	15833	AZ	Sandra Sellers	(602) 287-8066	28	18	10	18	64.3%	10
Steel	15823	NC	Margo Rizzo	(252) 759-4548	28	10	18	10	35.7%	18
Stoney	14349	NY	Paula Lurie	(516) 438-0822	28	21	7	21	75.0%	7
Suri	18269	CA	Katie Thoma	(650) 595-1861	28	10	18	10	35.7%	18
Vink	15834	VA	Polly Morgan	(757) 448-5912	28	10	18	10	35.7%	18
Weinstein	13033	CA	Jake VgOlong	(925) 830-7267	28	44	16	44	157.1%	16

Screen Failure Rate: 47%
Early Termination Rate: 46%
Completion Rate: 39%
Total Study Enrollment: 84%
CRFs in: 58%

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M99-114 Early Terminations

Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Backonja	4457	37	1	AE	uric nitrogen level high panic at 56
Baumel	4143	85	1	AE	nausea, etc.
	4148	78	10	AE	dizziness, weakness, heart palpitations, headaches, blurred vision
	4147	85	11	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
	4228	73	unk	AE	hypoglycemic episode
	4229	43			
	4230	57			
	4231	73			
Blon	4280	82			
Bronberg	4113	89	10	AE	nausea, etc.
	4115	45	5	AE	nausea, etc.
	4117	50	7	AE	nausea, etc.
	4118	49	10	AE	dizziness, vomiting, nausea
	4125	85	1	AE	extreme nausea
	4128	85			
DeBolt	4051	71	8	AE	nausea, etc.
	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	1st. nausea/vomit since 5/1, int. abd bloating & constipation, decr. urine stream since 8/26
	4057	72	18	AE	intermittent nausea and vomiting
	4058		3	AE	dizziness, lethargy, vivid dreams, insomnia, increased neuropathic pain
	4080	57			
Drucker	4001	72	3.5	AE	joint pain in lower extremities
	4002	71	3	SAE	palpitations
	4003	78	0.5	AE	blurred vision
	4005	48			
	4008	72	1	AE	nightmares and intense neuropathic pain after 1st dose, whole body numb, wobbly, weak after 2nd dose
Elaine	4241	80	1	AE	nausea, etc. (went to ER)
Forde	4321	67	5	AE	disturbing dreams/nightmares
Fried	4083	88	14	SAE	syncope episode related to historical atrial fibrillation (admitted to hospital 5/30)
	4087	74	4	AE	diarrhea, GI upset, fatigue, light-headedness (patient took every dose following a meal)
	4089	81	6	AE	dizziness
Gibson	4354	73	1.5	AE	nausea
	4358	31	27	AE	nausea and vomiting
	4367	32	12	AE	nausea and vomiting
Gleason	4184	81	1	AE	dizziness, disorientation
	4185	51			
	4187	70			
Haag	4337	43	5.5	AE	dizziness ~2hrs post-dose x 10 episodes
	4340	72	8	AE	difficulty falling asleep, awakening more frequently
	4341	85	36	AE	mental status changes
Hewitt	4311	52	8	AE	nausea and vomiting
Holmlund	4193	53	7	AE/SAE	vomiting, fatigue, broken pelvis
	4195	50	7	AE	nausea, vomiting
	4197	82	4	SAE	chest pain
Katka	4417	74	6	AE	nausea, vomiting
	CMW		7	AE	jaw pain, insomnia, increased BP, heart palpitations, tingling
	4419	81	46	AE	nausea and vomiting
Kipnes	4065	64	3.5	AE	nausea
	4068	55	25	AE	nausea
	4070	48	10	SAE	left arm pain
	4072	70	7	AE	nausea, etc.
	4075	74	2	AE	severe nausea, shakiness
Kisty	4178	52	8	AE	backache
	4501	55	8	AE	unsteady gait, nausea, indigestion
Kuge	4131	70	8.5	AE	nausea, etc.
	4153	86	5.5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 8/6-8/10)
McGill	4367	86	7	AE	nightmares, insomnia, nausea
	4380	58			
Shebani	4430	58	30	AE	stomach ache
	4451	60	18	SAE	chest pain, shoulder pain

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ABBT242697

M99-114 Early Terminations

	4405	66	1	AE	got sick after first day
	4456	87	7	AE	headaches, lightheadedness, depression, rectal bleeding, sleeplessness caused by stomach acid
	4482	55			
	4483	66			
	4493	61			
Simmons	4273	58	11	AE	GI ax, cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	89	10	AE	vomiting, nausea, headache, vivid dreams, diarrhea, chills
	4276	58	19	AE	nausea
	4277	56	9	AE	nausea, vivid dreams
Singer	4401	53		AE	angina secondary to coronary artery blockage
	4402	67	12	AE	dizziness, vomiting
	4403	57	25	AE	worsening insomnia
	4408	58	8	AE	vomiting
Strakosma	4038	59	3.5	AE	anxiety, etc.
	4040	57	7	AE	apprehensive, irritable, tension, headache, burning eyes, diarrhea, vivid dreams
	4041	51	1	AE	nausea, vomiting, diarrhea
Steel	4208	66	22	AE	light-headed, dizzy
	4210	73	9	AE	vomiting
	4215	80	10	AE	severe nausea
	4216	82			
Storey	4096	70	5.5	AE	nausea, etc.
	4100	56	3	AE	nightmares
Weinstein	4102	89			
	4020	73			
	4021	65	13	AE	coughing, sore throat, cold ex (want to ER)
	4024	63			
	4028	70			
	4459	79	8	AE	dizziness, nausea, diarrhea

[illegible]


ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED
DATE 01-11-2001 BY 60322 UCBAW

ABB T242699

ABB T242699

Collicott Deposition Exhibit 30

D's Exhibit GM

 Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
01/18/2001 09:25 AM

To: dsharma@dresources.com
cc:
bcc:
Subject: ABT-594

Good Morning

I am the Clinical Project Manager in the Analgesia Venture and can answer your questions about ABT-594. We are currently in Phase II of development having just completed a study for neuropathic pain. There is the potential that we may do an OA trial yet this year. Studies are being conducted in the US only at the present time. If you have any additional questions, please don't hesitate to email me.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Abbott Laboratories/Analgesia Venture

Forwarded by Marilyn J Collicott/LAKE/PPRD/ABBOTT on 01/18/2001 09:21 AM

Robin J Sabine

01/18/2001 09:08 AM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT,

EMAIL ADDRESS: dsharma@dresources.com

FIRST NAME: Deepak

LAST NAME: Sharma

ADDRESS 1: 1100 Winter Street

CITY: Waltham

STATE: MA

ZIPCODE: 02453

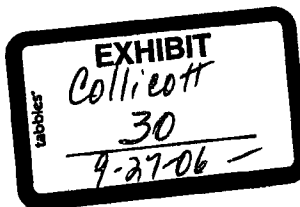
PHONE: 781-487-3715

OTHER: R&D Pipelin

I would like to ask about the status of ABT-594. What phase of clinical development has this compound reached and for what pain indications is it being developed (e.g. post-operative pain, osteoarthritis pain, etc) Also are clinical trials underway in both Europe and the United States?

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ABBT240417



Collicott Deposition Exhibit 31

P's Exhibit EK

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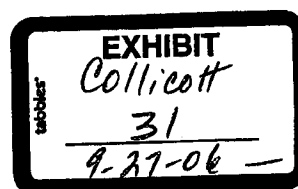
ABT-594

Descriptive Memorandum

February 2001

Abbott Laboratories

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ABBT246076

ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Currently, there is an unmet market need for novel neuropathic pain treatments such as ABT-594. Therefore, this compound is likely to be well received in this arena. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

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Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
TOTAL	\$351	21.7%	\$140	10.1%
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

Competition, Products in Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

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Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through (2 nd) subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tapexallin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

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Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epiibatidine analog
SIB-T1887	Sibla	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimolecular) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

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Product / Development Background**Scientific Rationale for ABT-594**

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 750ug BID, the maximum dose studied in this protocol. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 750ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients is anticipated to be included in the study.

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Considerations**Target Profile:**

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
 - 2) Treatment of post-herpetic neuralgia
 - 3) Treatment of neuropathic pain
 - 4) Treatment of chronic pain
 - 5) Treatment of cancer pain

Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

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Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2s is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

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CCM (ABT-594)
Annual Development Plan
Exhibit 1.5

Therapeutic Area	Neuroscience						
Indications	ABT-594 primary target indication is the treatment of neuropathic pain (NP). - ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator. - ABT-594 is effective in nociceptive pain and neuropathic pain. - ABT-594 is expected to have a better side effect profile than opioids, no tolerance, no abuse, and no DEA schedule. - Pre clinical data show ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in treatment models of pain. - ABT-594 has a unique mechanism of action which may enable use in combination with other analgesics as a multimodal approach. - Slow onset of action (approx. 1.5 - 3 hours) at low doses tested may suggest limited utility in acute pain types. - Favorable safety profile. - Oral formulation, BID dosing.						
Description							
Current Timeline	Milestones		Date				
	IND Filing		4Q1998				
	Phase I		3Q1997				
	Phase II		3Q1998				
	Phase III		4Q2001				
	NDA Filing		3Q2003				
	Launch		3Q2004				
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
	14.4	35.0	45.0	32.0	15.0	12.0	153.4

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 ating moderate to severe pain in several well characterized animal
 well as monotherapy.
 s.

Spending	\$5.
Project-to-Date-Spending (thru '00)	97.3
2001 Current Projection (Plan)	35.0*

* See page 2 for detail.

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Collicott Deposition Exhibit 32

P's Exhibit EL

Part 1

Project Review

ABT-089 and ABT-594

February 2, 2001

EXHIBIT
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32
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ABBT 0002314

Project Review

◦ ABT-089

REDACTED

◦ ABT-594

- Overview, upcoming milestone: June 2001
- Follow-on strategy

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Neuronal Nicotinic Receptor (NNR) Program

- Scientific leadership position for Abbott
- An emerging diversity of receptors
- Multiple potential therapeutic targets

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ABT-089

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ABBT 0002317

ABT-089

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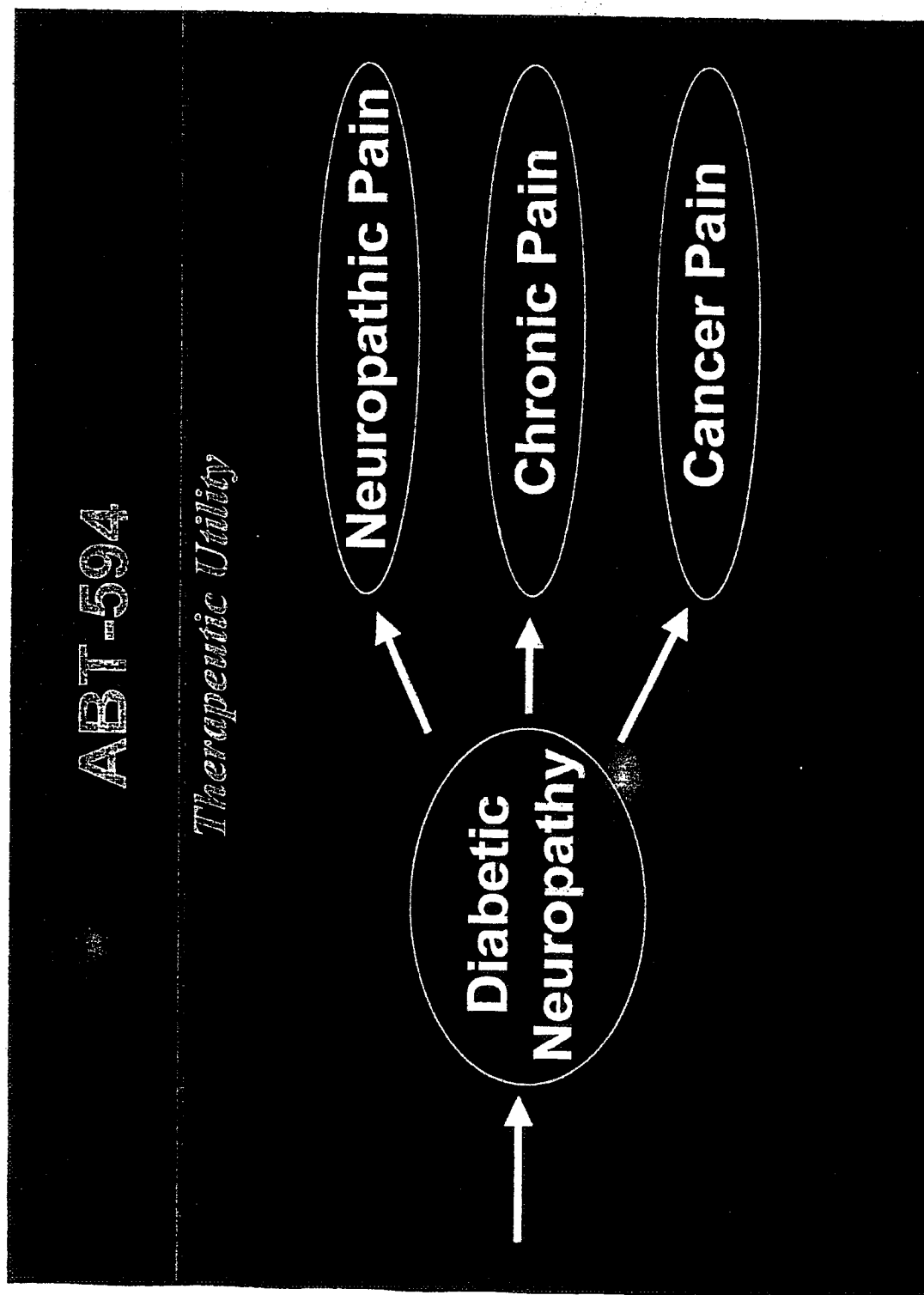
ABT-594

Overview

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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Collicott Deposition Exhibit 32

P's Exhibit EL

Part 2

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ABBT 0002358

ABT-594 Project Review February 2, 2001

Introduction

Chris Silber

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ABBT 0002359

ABT-594 Project Review

Agenda

- Introduction Chris Silber
- Pharmacological Profile Jim Sullivan
- Clinical Overview Bruce McCarthy
- Commercial Assessment Andrea Landsberg
- Go/No Go Process Bruce McCarthy
- Follow-On Strategy Mike Meyer

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ABT-594

Overview

- First-in-class
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Pain Prevalence

- 22% primary care patients worldwide have persistent pain
- Neuropathic pain
 - 20% of diabetics
 - 40% of HIV infected
 - 36% of cancer patients

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Pain Therapeutics Market

- \$12 billion in sales of key classes (NSAIDs, COX-2s, opioids, non-opioids)
- \$700 million in sales of key neuropathic pain compounds
 - use largely off-label
 - low cost generics

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Neuropathic Pain

Treatment

Some efficacy

(at best 40% vs. 20% placebo)

- Tricyclic antidepressants
 - Amitriptyline, desipramine, etc.
- Anti-epileptic drugs
 - Carbamazepine
 - Gabapentin (Pregabalin)
 - Topiramate, others
- Sodium channel blockers
 - Lidocaine
- Opioids
 - Tramadol

No efficacy

- SSRIs
- NSAIDs/COX-2

**Broad-Spectrum, Non-Opioid Analgesic Activity
by Selective Modulation of Neuronal Nicotinic
Acetylcholine Receptors**

A.W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon,
D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz,
A. H. Dickenson, R. D. Porsoit, M. Williams, S. P. Arneric

SCIENCE • VOL. 279 • 2 JANUARY 1998

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Development Strategy

Acute

Post-dental surgery
Sprains and strains
Acute back pain
Trauma
Post-general surgery
Post-orthopedic surgery
Dysmennorrhea
Renal colic
Biliary colic
Pancreatitis
Infections

Neuropathic

Diabetic polyneuropathy
Idiopathic polyneuropathy
Alcoholic polyneuropathy
Drug-induced polyneuropathy
HIV predominantly sensory neuropathy
Back pain
Cancer pain
Trigeminal neuralgia
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
Complex regional pain syndromes (I, II)
Atypical facial pain
Phantom limb pain

Chronic Nociceptive

Osteoarthritis
Chronic back pain
Rheumatoid arthritis
Cancer pain
Fibromyalgia
Sickle cell disease
TMJ disorder
Bursitis
Tendinitis
Chronic visceral pain

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ABBT 0002366

Development Strategy

Choose Portals of Entry

Molar

Extraction

Acute Pain



**Peripheral
Neuropathy**

Neuropathic Pain



Osteoarthritis

**Chronic Nociceptive
Pain**



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ABT-594

Current Label Target

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

Upside Claim

- Neuropathic Pain
- Post herpetic neuralgia
- OA Pain
- Chronic Pain
- Cancer Pain

General Pain Claim

- Not viable due to 1.5 hour onset

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ABT-594

Go/No Go Process

- Decision analysis (DSG) will be used as a tool to determine milestone criteria
 - Efficacy and safety
 - Titration effects
 - Dose selection
 - Indications
 - Market research

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ABT-594

Phase III Clinical Plan

	U.S.	Europe	Japan
Diabetic neuropathy	2 (n=1200)	2 (n=1200)	1 (n=300)
Long-term safety	1 (n=500)	1 (n=500)	-
Gabapentin comparator	-	1 (n=320)	-
Other neuropathic pain (Phase 3B) post herpetic neuralgia, sciatica	2 (n=600)	-	-

	<u>01</u>	<u>02</u>	<u>03</u>	<u>Total</u>
Cost (\$ million)	6.1	59.6	55.7	121.4

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ABT-594*Phase 2 to 3 Transition*

Milestone review	6/01
End of Phase 2 package/request	9/01
Start manufacture Phase 3 supplies	9/01
Ship first Phase 3 supplies	2/02
Initiate Phase 3	3/02
Regulatory filings	9/03

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ABT-594

Overview

- First-in-class
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ABT-594 Project Review

February 2, 2001

Pharmacological Profile

Jim Sullivan

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ABBT 0002373

ABT-594: Preclinical Pharmacology

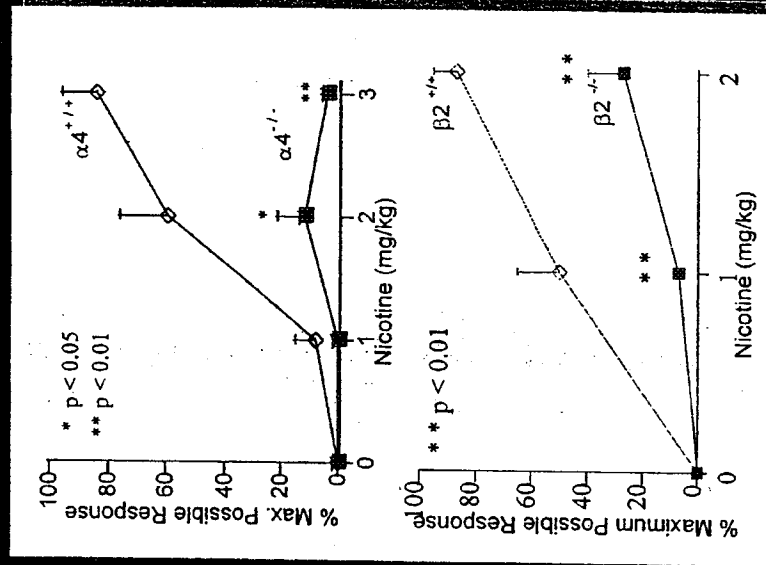
- Rationale for NNRs and pain
 - Knockout, antisense and pharmacological validation
- *in vitro* and *in vivo* profile of ABT-594
 - Efficacy
 - Safety

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ABBT 0002374

NNRs for Pain: Role of $\alpha 4$ and $\beta 2$ NNRS Established Using Knockout Mice

In either $\alpha 4^{-/-}$ or $\beta 2^{-/-}$ mice, neither nicotine nor epibatidine was active in the hot plate assay (supraspinal mechanism)



Marubio, et al. *Nature* 1999 398, 805-810.

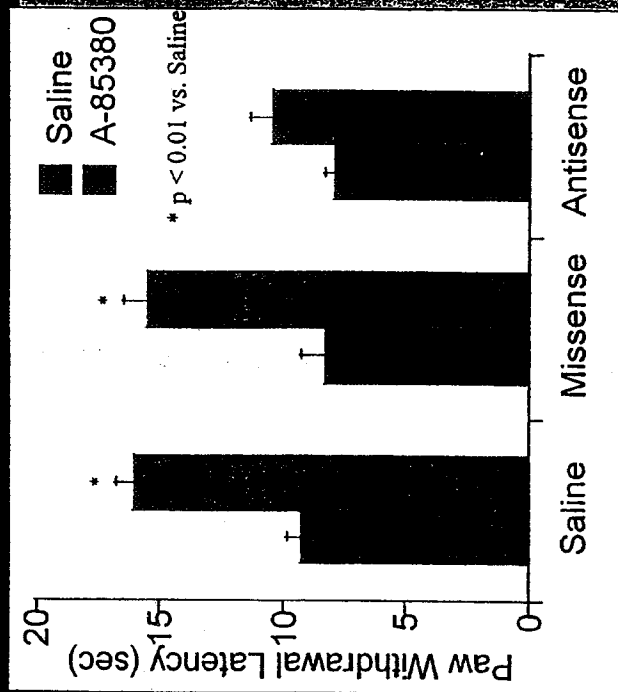
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ABBT 0002376

NNRs for Pain: Target Validation Using $\alpha 4$ Antisense

$\alpha 4$ Antisense Treatment Attenuates Antinociception in the Hot Box Model of Acute Thermal Pain

- Rats received either a saline, missense, or antisense continuous i.c.v. infusion (0.75 nmol/hr) for 7 days
- Rats were evaluated in a crossover design in the hot box model of acute thermal pain



Bither, et. al, *Brain Res.* 871: 66, 2000

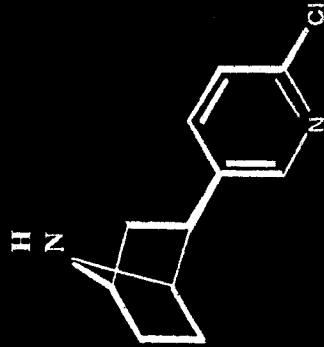
Target Validation: NNR Agonists Are Analgesic

- NNR agonists are -
 - Antinociceptive (capable of raising nociceptive thresholds in naïve animals)
 - Antihyperalgesic (capable of reversing the reduction in nociceptive thresholds following injury)



- Epibatidine (key discovery)

- 200x more potent than morphine
- Non-opioid
- Potent NNR agonist
- BUT highly toxic



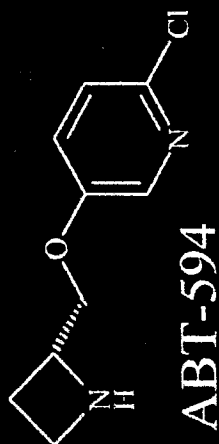
Badio and Daly, *Mol. Pharmacol.*
45: 563, 1994.

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ABBT 0002378

NNRs and Pain: ABT-594

Goal



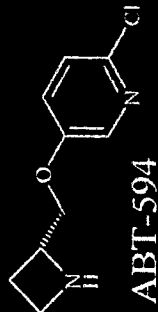
- Maintain broad spectrum analgesic efficacy of epibatidine
 - Maintain potency at $\alpha 4$ containing NNRs
- Decrease side-effect liabilities by decreasing activity at
 - Neuromuscular junction nicotinic receptors ($\alpha 1\beta\delta\gamma$)
 - Ganglionic NNR subtypes ($\alpha 3\beta 4$, $\alpha 3\alpha 5\beta 2\beta 4$)

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ABBT 0002379

ABT-594 is a More Selective NNR than Epibatidine in Radioligand Binding Studies

Binding Site (K _i ; nM)	Epibatidine	ABT-594
Cytisine Binding Site ($\alpha 4\beta 2$)	0.042	0.037
BTX Binding Site (Peripheral) ($\alpha 1$)	2.4	16,600



- ABT-594 retains potency of epibatidine at the $\alpha 4\beta 2$ binding site
- ABT-594 is > 5000-fold less potent than epibatidine at the peripheral neuromuscular junction nicotinic receptor

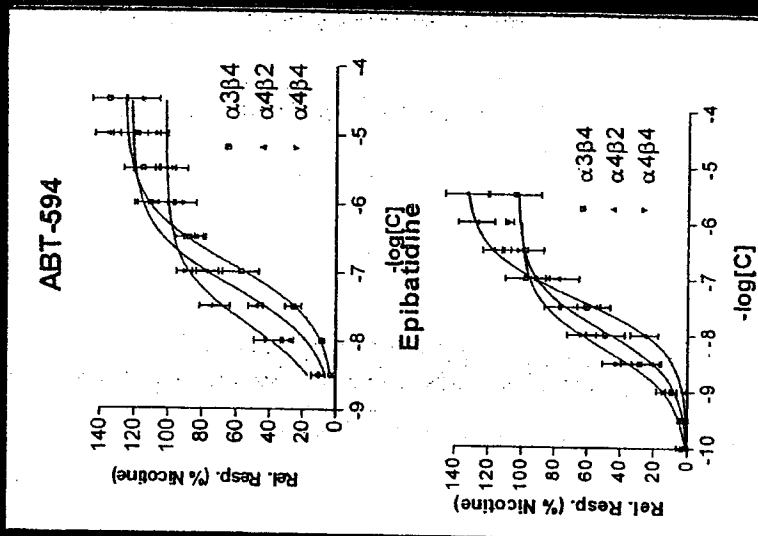
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ABBT 0002380

In Vitro Functional Profiles of ABT-594 and Epibatidine

Functional Activity

- Rank order of potency
 - ABT-594: $\alpha 4\beta 4 \sim \alpha 4\beta 2 > \alpha 3\beta 4$
 - Epibatidine: $\alpha 4\beta 4 \sim \alpha 3\beta 4 \sim \alpha 4\beta 2$
- ABT-594 displays modest $\alpha 4$ vs $\alpha 3\beta 4$ selectivity
 - Compounds with greatly improved selectivity have been identified

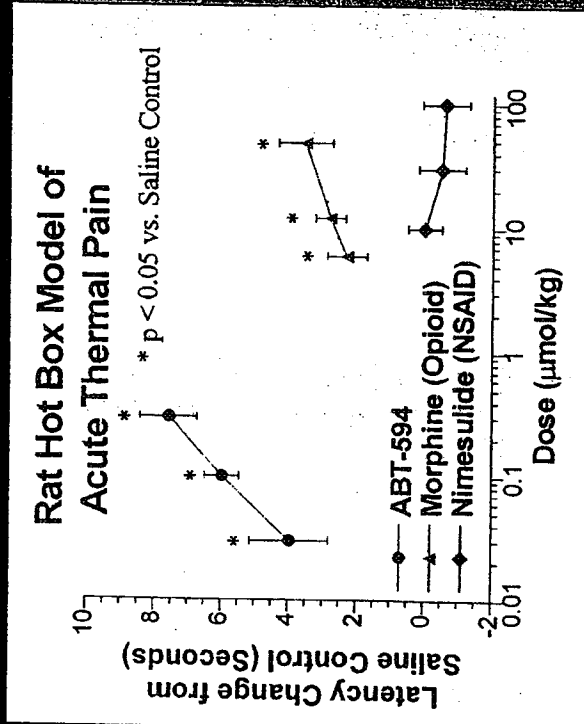


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ABBT 0002381

ABT-594: In Vivo Efficacy in Models of Acute Thermal Pain

- ABT-594 is potent and efficacious in the Hargreaves Hot Box model of thermal nociception
- Onset of Efficacy = < 30 min
- Duration of efficacy ~ 2 hrs
- The effects of ABT-594 are blocked by the nicotinic antagonist mecamylamine, but not by the opioid antagonist naloxone

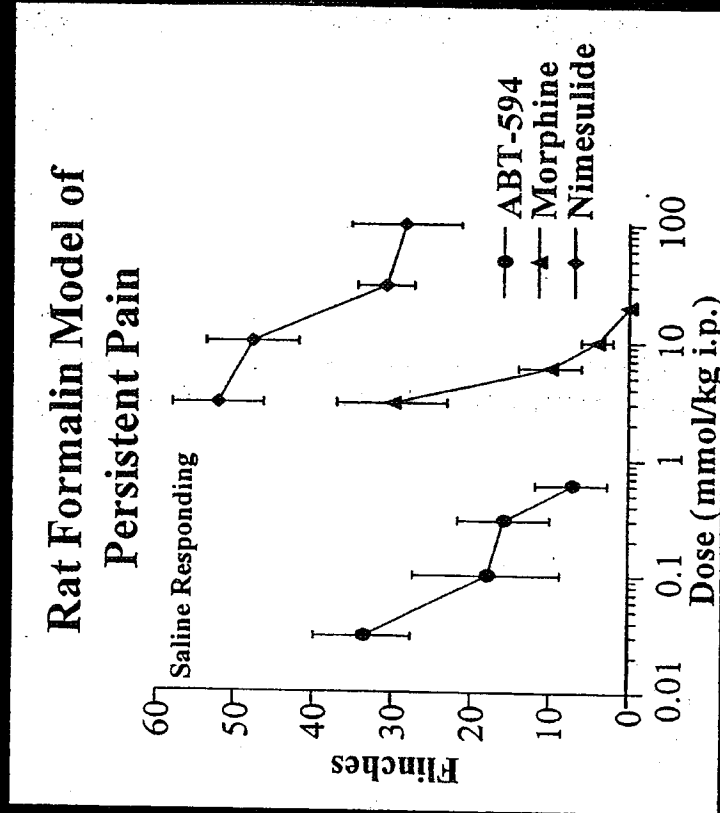


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ABBT 0002382

ABT-594: In Vivo Efficacy in Models of Persistent Pain

- ABT-594 exhibits comparable efficacy and 50-fold greater potency than morphine in Phase II of the formalin model of persistent chemical pain
- ABT-594 is active upon both i.p. and oral administration

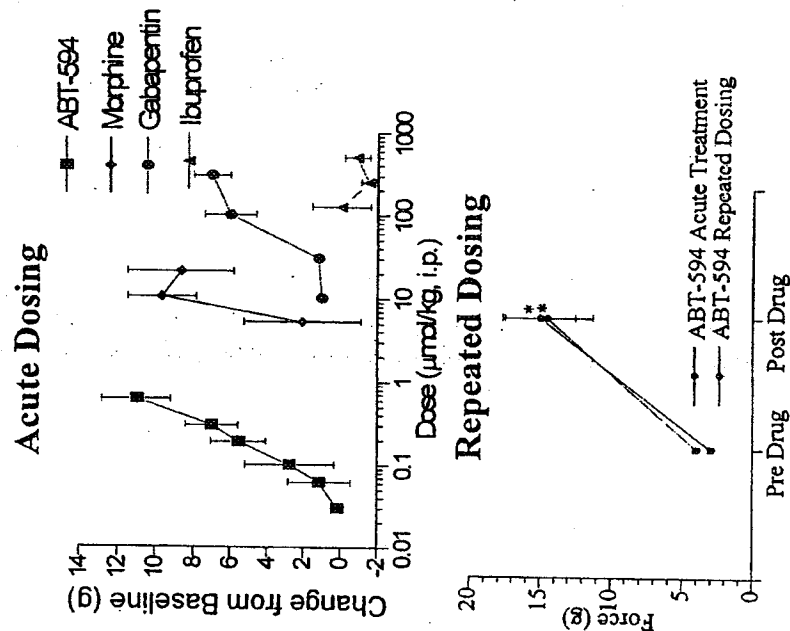


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ABBT 0002383

ABT-594: In Vivo Efficacy in Models of Neuropathic Pain

- ABT-594 exhibits comparable efficacy and enhanced potency vs. known efficacious agents in models of neuropathic pain
- Efficacy observed at ~ 3 ng/ml
- ABT-594 retains efficacy following repeated administration
- Efficacy observed in rodent model of diabetic polyneuropathy



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ABBT 0002384

ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 μ mol/kg)	+++ (0.1 μ mol/kg)	+++ (0.03 μ mol/kg)
Celecoxib	++ (30 μ mol/kg)	+ (30 μ mol/kg)	0
Morphine	+++ (3 μ mol/kg)	+++ (10 μ mol/kg)	++ (3 μ mol/kg)

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

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ABBT 0002386

How do NNR Agonists Produce Analgesia?

- Mouse knockouts support role of $\alpha 4$ and $\beta 2$
 - Key differences between pain type
- Role for $\alpha 4$ subtype in acute thermal pain (activation of descending inhibitory pathways)
 - Antisense studies
 - Site injection studies
 - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

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ABBT 0002386

ABT-594: Preclinical Assessment of Side Effect Liabilities

- **Emesis**
 - Emesis observed in monkey at 9x efficacious plasma levels
 - Emesis observed in dogs at efficacious plasma levels
 - Ferret model developed in response to early clinical data
 - Correlation established between activity at $\alpha 3\beta 4$ NNRs and emesis
- **CV**
 - No effects on hemodynamics at 30X efficacious plasma levels
- **Dizziness: no validated preclinical models exist**
 - Effects on balance, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing
- **ABT-594 displays a reduced propensity for morphine-like side effects of:**
 - Constipation
 - Respiratory Depression
 - Sedation

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ABBT 0002387

ABT-594: Summary of Preclinical Findings

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NNRs and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
 - Constipation
 - Respiratory depression
 - Sedation
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

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ABBT 0002388

**ABT-594 Project Review
February 2, 2001**

Clinical Overview

Bruce McCarthy

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ABBT 0002389

ABT-594

Take Home Messages

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
 - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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ABBT 0002390

ABT-594

**Definitely NOT a take home
message for today:**

*ABT-594 will satisfy the unmet medical need
in pain management*

*ABT-594 will not satisfy the unmet medical
need in pain management*

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ABBT 0002391

Collicott Deposition Exhibit 32

P's Exhibit EL

Part 3

ABT-594

Clinical development

- ❖ **Current pain management**
- **Development strategy: bench to bedside**
- **Clinical trial results**

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ABBT 0002392

Classification of Pain

Pain Categories

Noiceptive

Acute

Post-dental & post-surgical Pain
Trauma
Pancreatitis
Infections

Chronic

Osteoarthritis
Rheumatoid arthritis
Fibromyalgia
Chronic viscearal pain

Neuropathic

Acute

Compression neuropathy

Chronic

Diabetic polynuropathy
Idiopathic polynuropathy
Alcoholic polynuropathy
Drug induced polynuropathy
HIV predominantly sensory neuropathy
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
CRPS type I and II
Atypical facial pain
Phantom limb pain

Cancer pain
Back pain

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ABBT 0002393

Classification of Pain

Pain Epidemiology

• **Chronic pain**

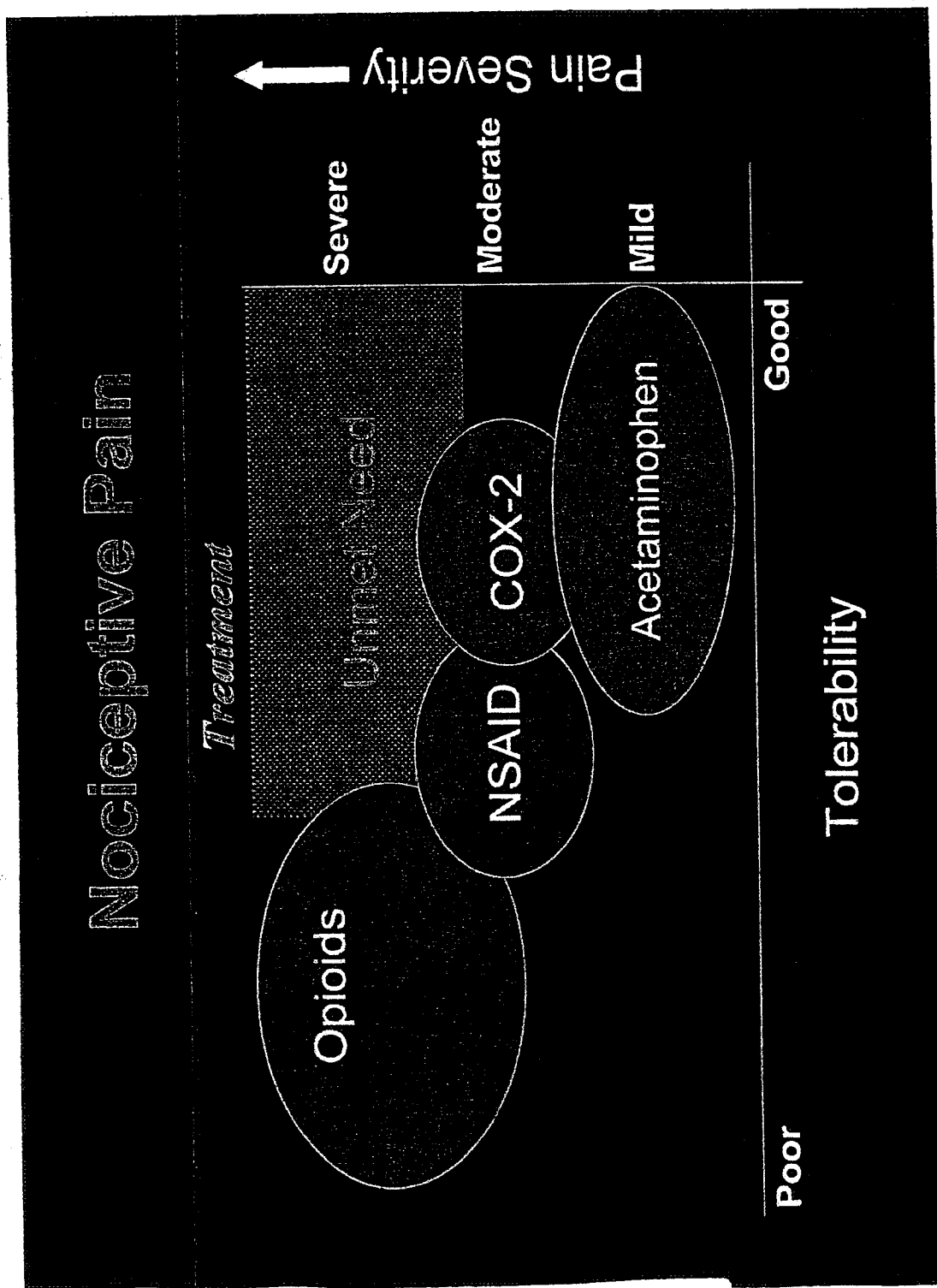
- 20% U.S. population: any chronic
- 22% worldwide: persistent pain

• **Neuropathic pain**

- 20% of diabetics
- 40% of HIV infected
- 36% of cancer

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ABBT 0002394



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ABBT 0002396

Nociceptive Pain

Treatment Adverse Events

OxyContin
Osteoarthritis
20 mg q12

OxyContin²

Ultram¹
50-100 mg

Event

23%

27%

13%

20%

23%

41%

12%

23%

23%

32%

N/A

16%

Somnolence

N/A

Dizziness

31%

Nausea

34%

Vomiting

13%

Constipation

33%

Pruritis

N/A

N/A

¹ Chronic non-malignant pain, up to 30 days (label)

² "Clinical trials" (label)

N/A - Not Available

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ABBT 0002396

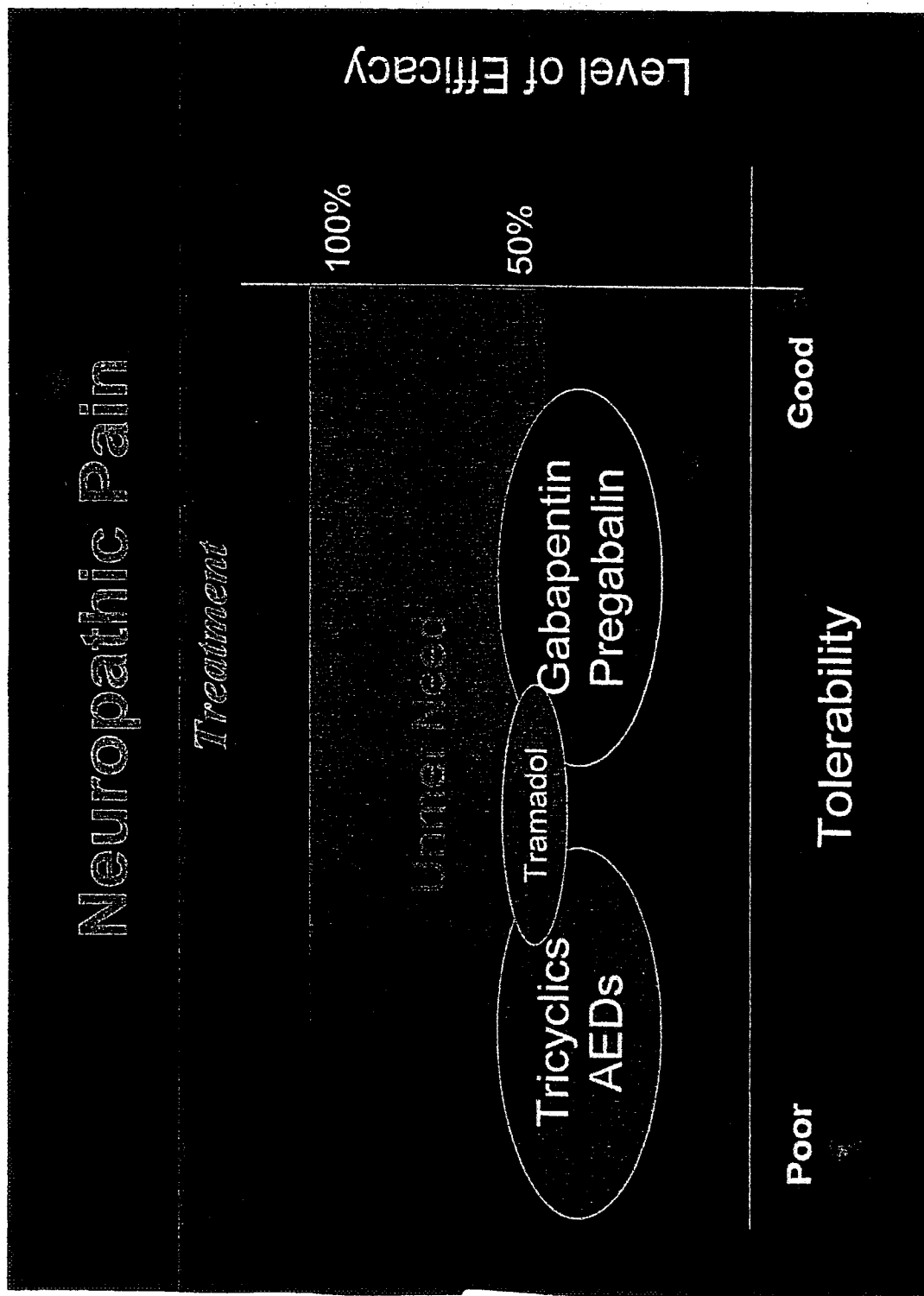
Neuropathic Pain

Overview

- **Characteristic symptoms**
 - Spontaneous: dysesthesia, shooting pains
 - Evolved: allodynia, hyperpathia
- **Pathophysiology**
 - Associated with peripheral nerve injury
 - Abnormalities develop over time in the PNS and CNS
- **Treatment**
 - Tricyclic and other "antidepressants"
 - Antiepileptic drugs
 - Sodium channel blockers (lidocaine)
 - Opioids
 - All minimally effective

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ABBT 0002397



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Neuropathic Pain

Treatment Adverse Events Rates

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A	8%	5%
Somnolence	66%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

¹ Max, 1987 (n=29)
N/A - Not Available

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ABBT 0002399

ABT-594

Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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ABBT 0002400

ABT-594

Proof of Principle

What characterizes an innovative analgesic?

Spectrum of activity

Time of onset/duration

Level of efficacy

Safety/efficacy ratio

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ABBT 0002401

ABT-594

Spectrum of Activity: Where to Start?

Acute

Post-dental surgery
Sprains and strains
Acute back pain
Trauma
Post-general surgery
Post-orthopedic surgery
Dysmenorrhea
Renal colic
Biliary colic
Pancreatitis
Infections

Neuropathic

Diabetic polyneuropathy
Idiopathic polyneuropathy
Alcoholic polyneuropathy
Drug-induced polyneuropathy
HIV predominantly sensory neuropathy
Back pain
Cancer pain
Trigeminal neuralgia
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
Complex regional pain syndromes (I, II)
Atypical facial pain
Phantom limb pain

Chronic Nociceptive

Osteoarthritis
Chronic back pain
Rheumatoid arthritis
Cancer pain
Fibromyalgia
Sickle cell disease
TMJ disorder
Bursitis
Teninitis
Chronic visceral pain

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ABBT 0002402

ABT-594

Choose Portals of Entry

Molar
Extraction



Acute Pain

Peripheral
Neuropathy



Neuropathic Pain

Osteoarthritis



Chronic Nociceptive
Pain

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ABBT 0002403

ABT-594

Initial Profile

- **Preclinical promise**

- Efficacy for all types of pain
- Challenges

- **Current characteristics**

- Analgesic potential demonstrated in molar extraction, neuropathic pain and osteoarthritis
- Onset (T_{\max} ; tolerability) appears to exclude rapid relief of pain (“acute pain”)

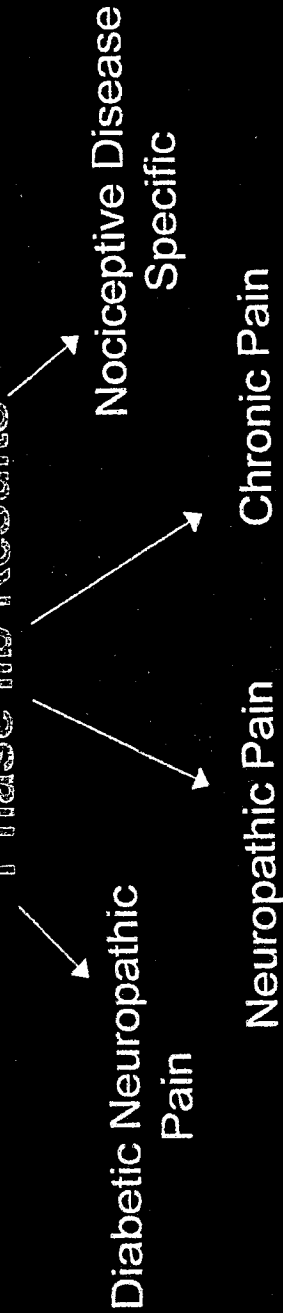
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ABBT 0002404

ABT-594

Future Regulatory Strategy

Phase IIb Results



+/- Publication Strategy/Phase IV (e.g.)

- Post-herpetic neuralgia
- Nociceptive pain
 - o Osteoarthritis
 - o Low back pain

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ABBT 0002405

ABT-594

Clinical development

- Current pain management
- Development strategy: bench to bedside

❖ Clinical trial results

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ABBT 0002406

ABT-594

Pharmacokinetics and Metabolism

- Half-life ($t_{1/2}$): about 8-12 hours
- Dose proportional kinetics
- AUC, C_{\max} similar across formulations (solution, SEC, HGC)
- AUC, C_{\max} similar with/without food
- T_{\max} varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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ABBT 0002407

ABT-594

ABT-594's analgesic potential demonstrated in:

Molar Extraction

Neuropathic Pain

Osteoarthritis

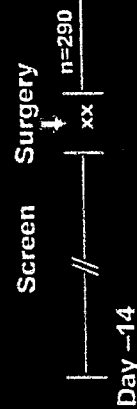
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ABBT 0002408

Molar Extraction Study

Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo
Single dose	

- Third molar extraction

- Outcome measures:

Pain relief (PR)

Categorical scale:

0	1	2	3	4
none	a little	some	a lot	complete

- Power: 70% to detect an effect similar to acetaminophen plus codeine Solution

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ABBT 0002409

Molar Extraction Study

Outcome Measures

Pain Relief (PR)

— Categorical scale: 0 none 1 a little 2 some 3 a lot 4 complete

Total Pain Associated Relief (TOTPAR)

— Area under the curve for PR (0-6 hours)

Pain Intensity (PI)

— Categorical scale: 0 none 1 mild 2 moderate 3 severe

— Visual Analog Scale

no pain ————— worst pain

Stop Watch Model

— Time to "perceptible" and "meaningful" relief

Time To Rescue Medication

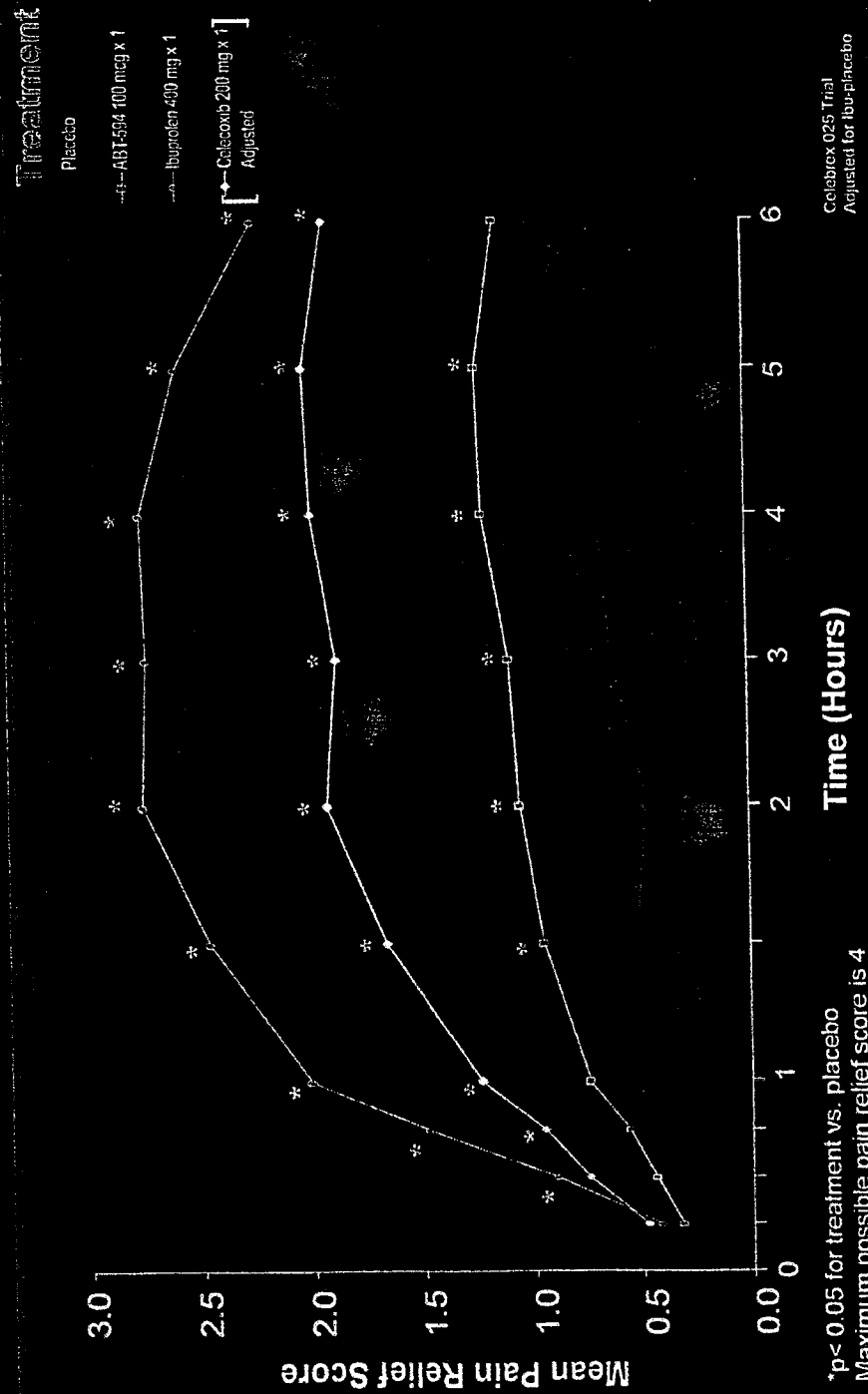
Patient Global

— Rate medication: 1 poor 2 fair 3 good 4 excellent

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ABBT 0002410

ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



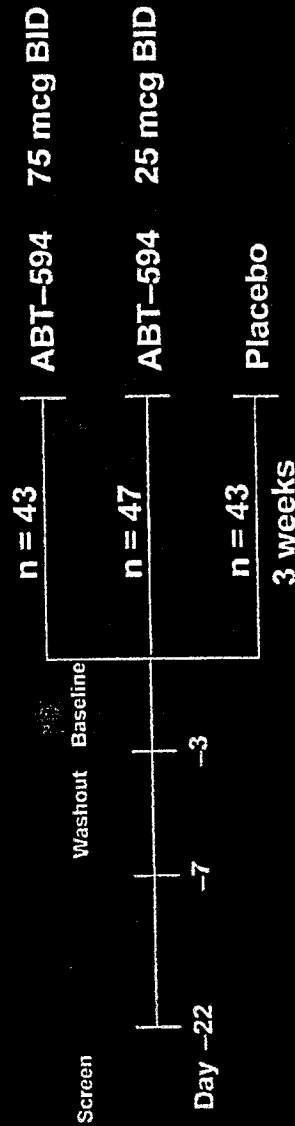
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ABBT 0002411

Neuropathic Pain Pilot

Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
 - 52% idiopathic
 - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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ABBT 0002412

Neuropathic Pain Pilot

Outcome Measures

◦ Pain Intensity (PI)

– Categorical Scale:

0 none 1 mild 2 moderate 3 severe

– Visual Analog Scale:
(0-100 mm)

no pain | worst possible

◦ Neuropathic Pain Scale (NPS)

– 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp

1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	----

The most sharp sensation imaginable ("like a knife")

◦ Patient Global (PG)

– Rate Medication:

1 poor 2 fair 3 good 4 excellent

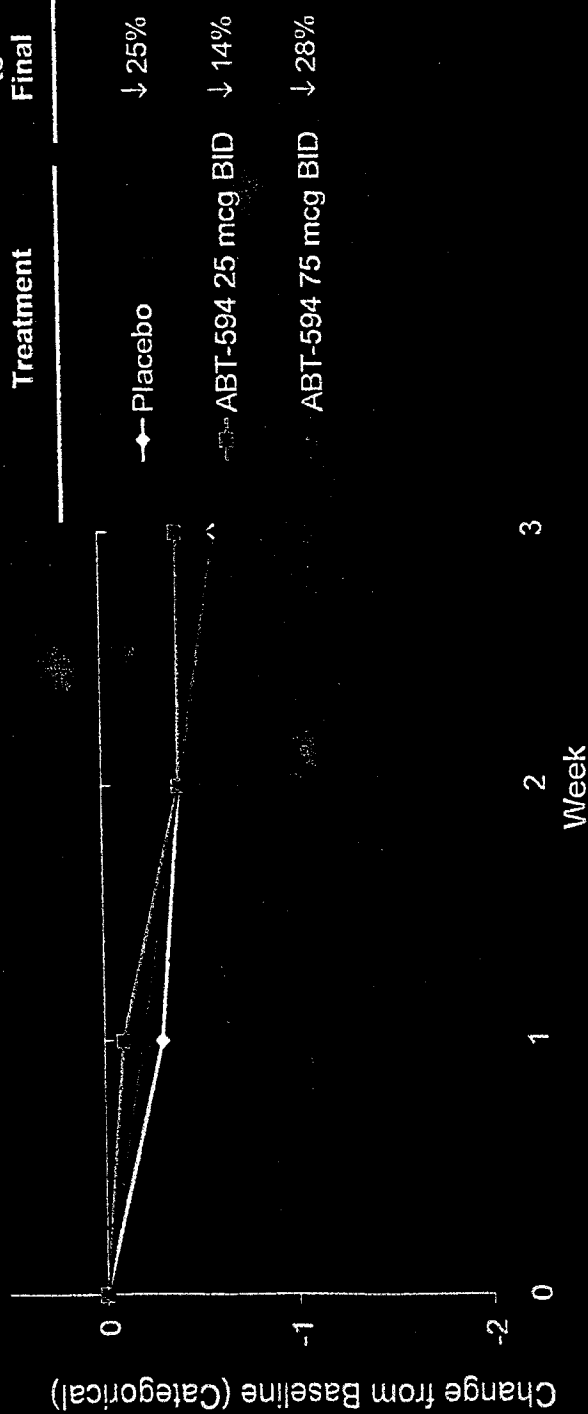
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ABBT 0002413

ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain

Change:
Baseline
to
Final

Treatment



Model based, ITT
LOCF
833

Maximum possible decrease for 75 mcg BID was 2.5

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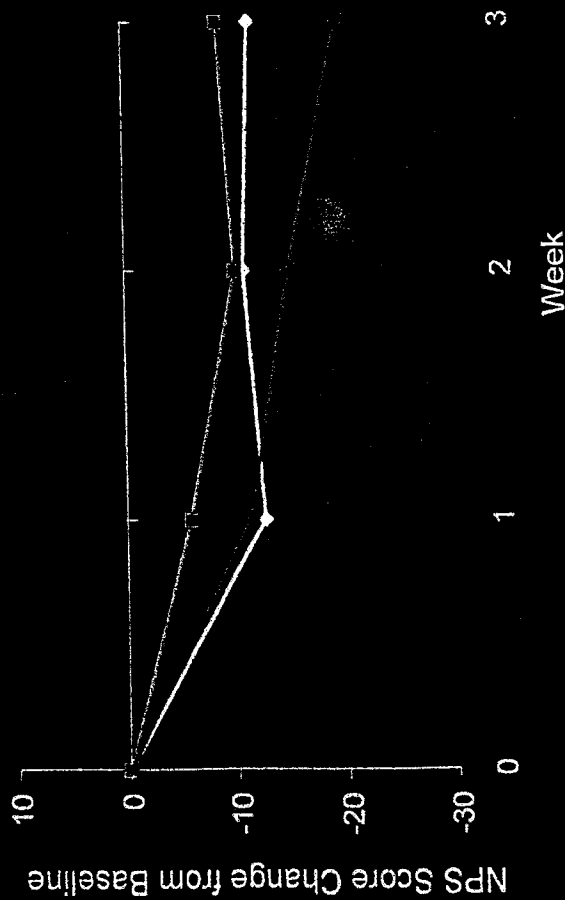
ABBT 0002414

ABT-594 75 mcg BID Reduces the NPS More Than Placebo

Change:
Baseline
to
Final

Treatment

- Placebo
- ABT-594 25 mcg BID
- ABT-594 75 mcg BID



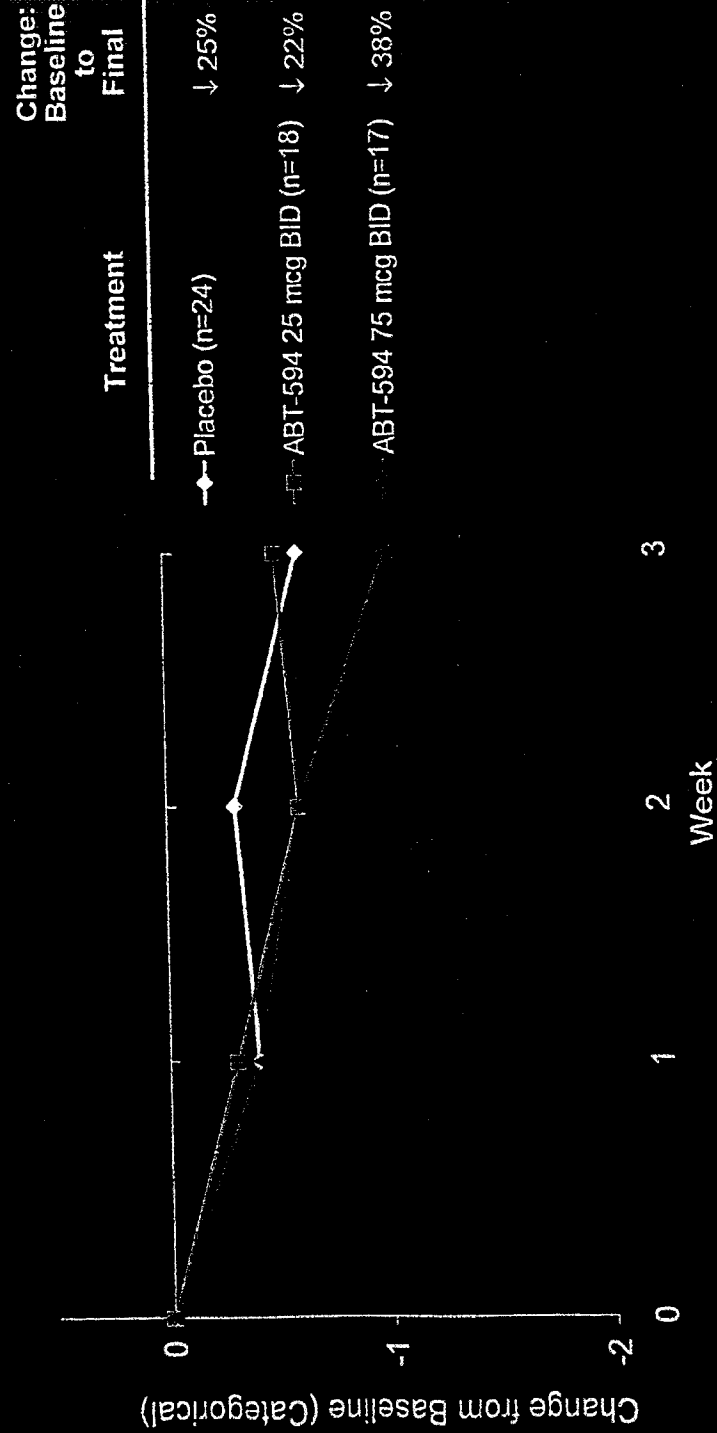
Model Based, ITT
LOCF
033

Maximum possible decrease for 75 mcg BID was 59

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ABBT 0002415

ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy



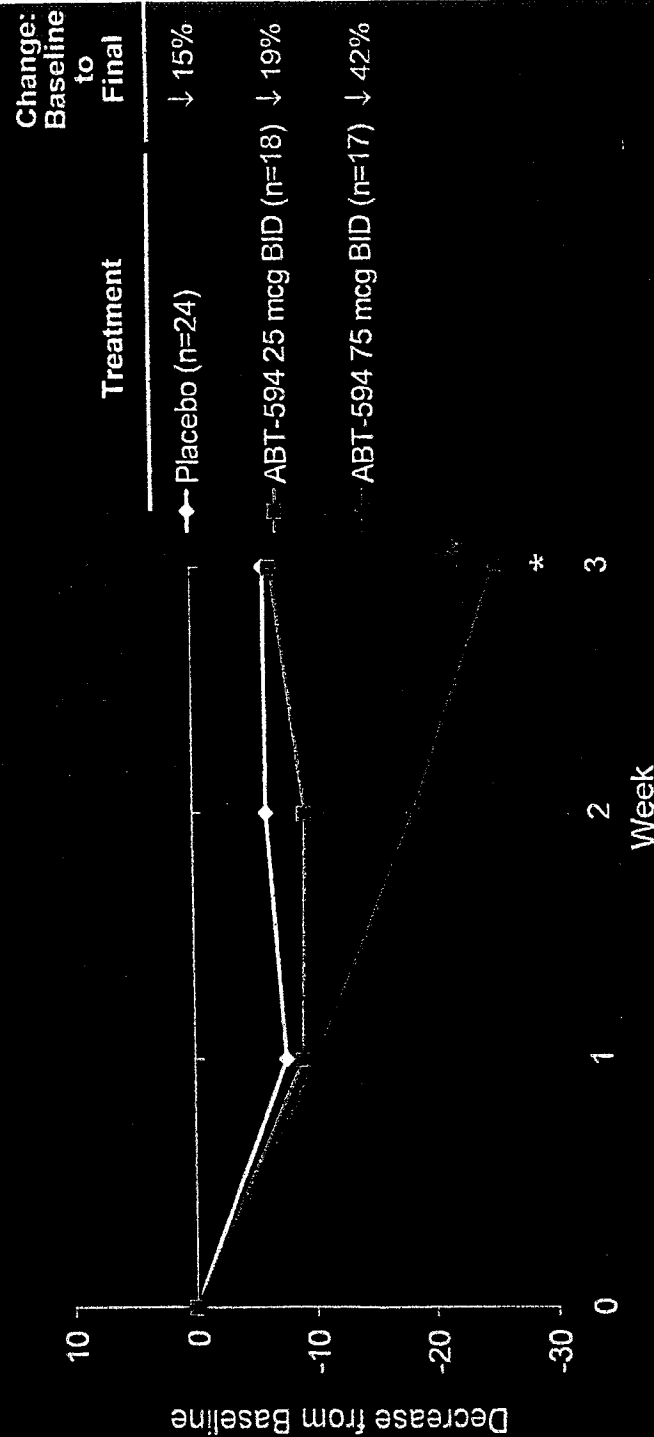
Maximum possible decrease for 75 mcg BID was 2.6

Model based, ITT
LOCF
833

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ABBT 0002416

ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy



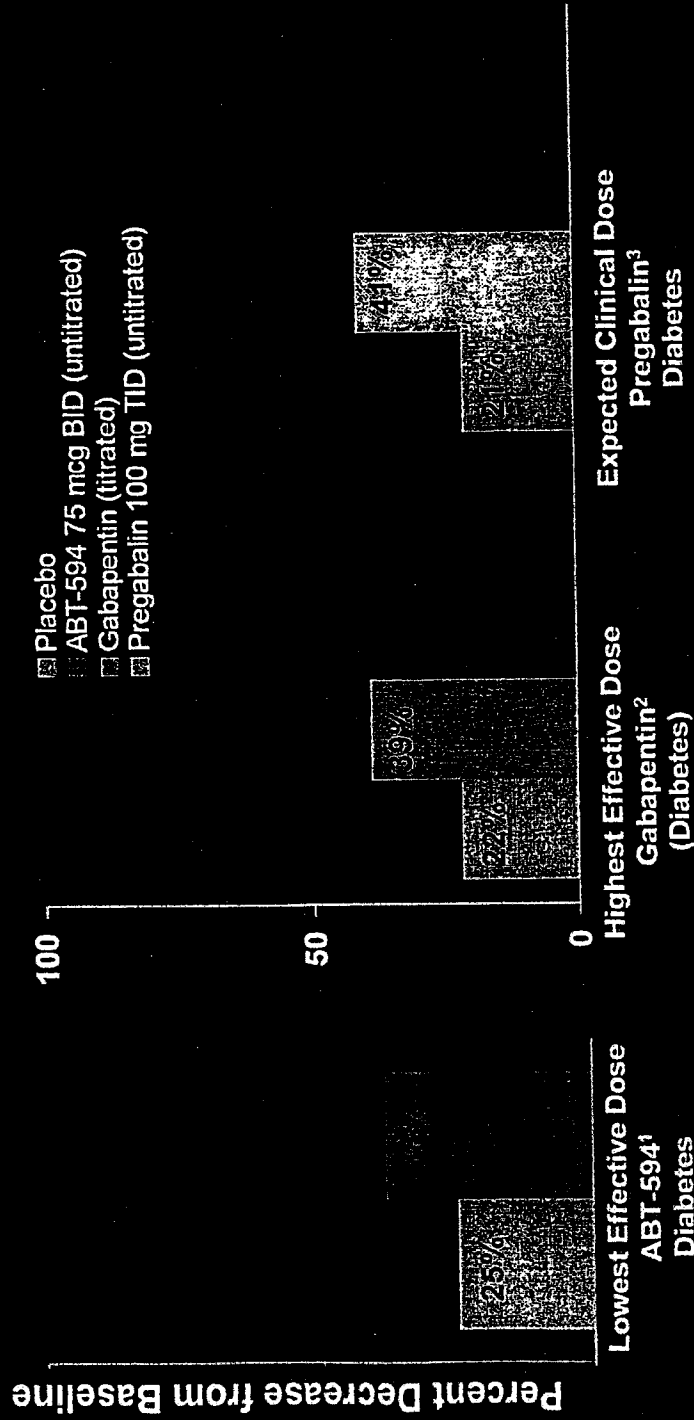
Model Based, ITT
LOCF
833

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ABBT 0002417

ABT-594 75 mcg BID has a Similar Effect To Gabapentin

ABT-594 vs. Gabapentin and Pregabalin



¹ 4-point categorical scale final vs. baseline
² 11-point Likert Scale week 8 vs. baseline
³ 11-point Likert scale week 5 vs. baseline

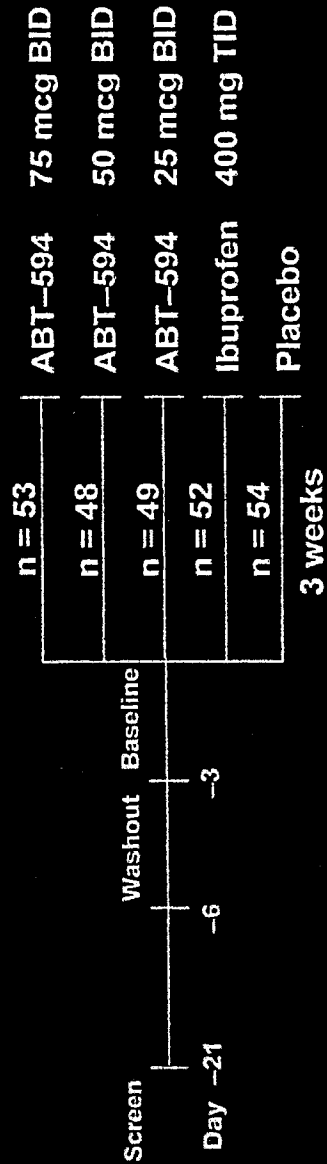
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ABBT 0002418

Osteoarthritis Pain Pilot

Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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ABBT 0002419

Osteoarthritis Pain Pilot Study

Outcome Measures

• Pain Intensity (PI)

– Categorical Scale:

0	1	2	3
none	mild	moderate	severe

– Visual Analog Scale (VAS):



• WOMAC

- Pain (0-500)
- Stiffness (0-200)
- Function (0-1700)

Total (0-2400)

• Patient Global

– Rate Medication:

1	2	3	4
poor	fair	good	excellent

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ABBT 0002420

Osteoarthritis Pain Pilot Study

WOMAC

Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain

extreme
pain

Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness

extreme
stiffness

Function

What degree of difficulty do you have...

- Descending stairs?
- Rising from bed?

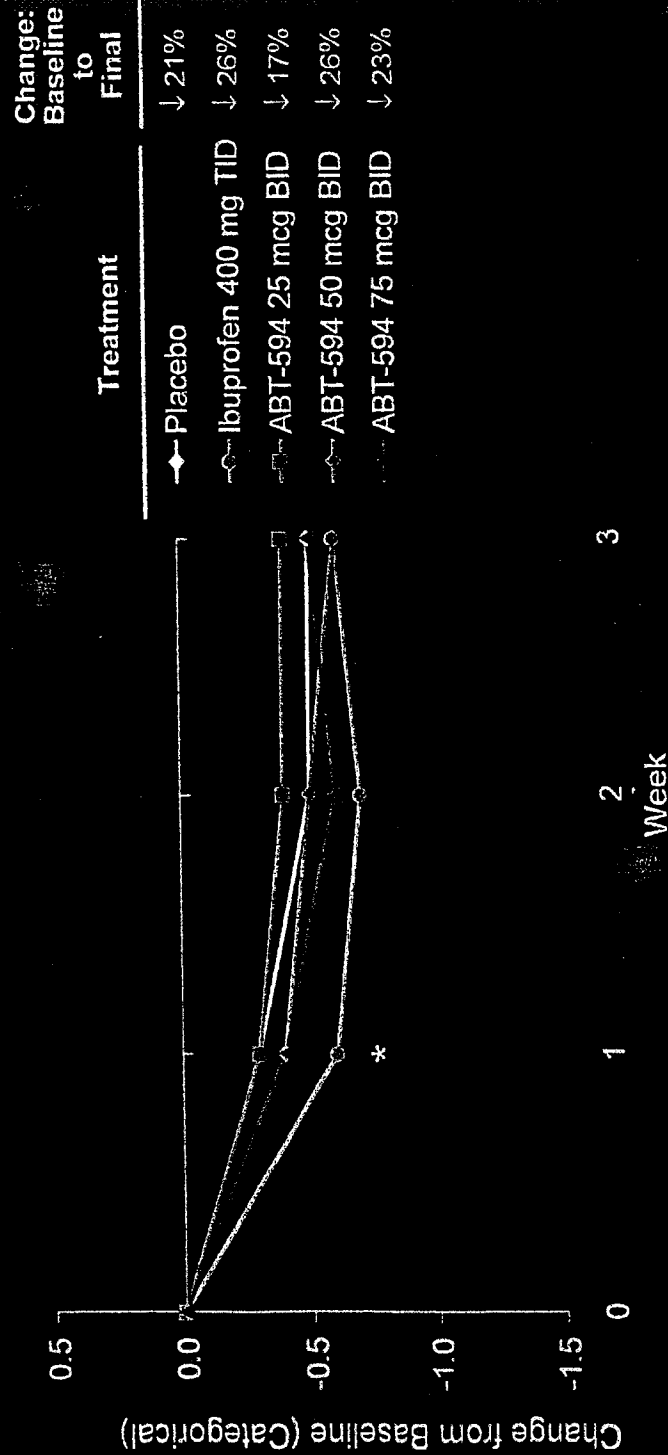
no difficulty

extreme
difficulty

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ABBT 0002421

ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis



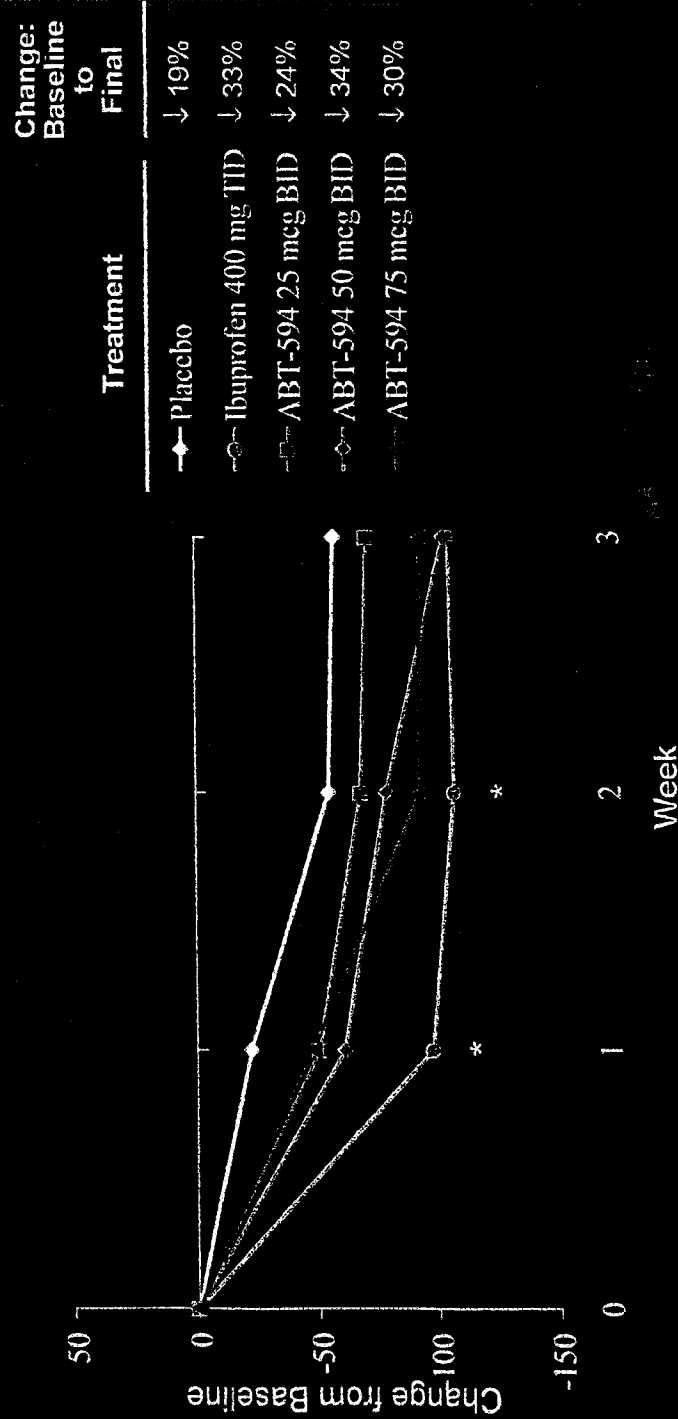
Model based, ITT
LOCF
U26

* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 2.2

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ABBT 0002422

ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis



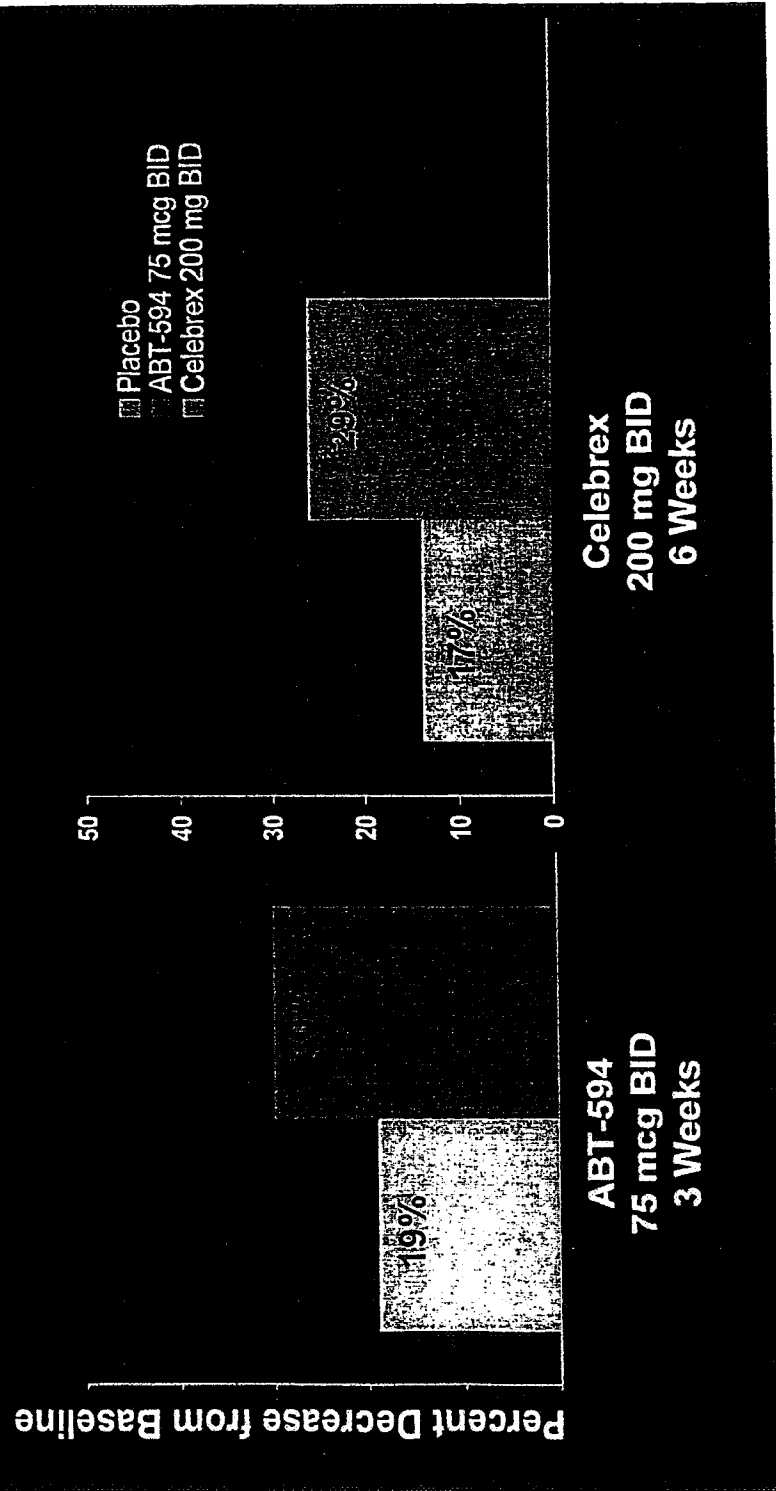
* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 305

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ABBT 0002423

ABT-594 75 mcg BID Has An Effect Similar to Celebrex

WOMAC Pain Decrease from Baseline



ABT-594

Phase IIIa Efficacy Conclusions

- Analgesic Potential Demonstrated

- Molar Extraction

- Significance vs. placebo starting at 1.5 hours

- Neuropathic Pain

- 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy

- Osteoarthritis Pain

- 75 mcg BID may be lowest effective dose as judged by the WOMAC pain sub-score

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ABBT 0002425

ABT-594 Safety

Phase IIIa Adverse Events

- Characteristic AEs
 - Nausea
 - Vomiting
 - Dizziness
- AEs attenuate after repeated administration

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ABBT 0002426

Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 ² 75 mcg BID
Confusion	N/A	N/A	5%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	23%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	N/A

¹ Max, 1987 (n=29)² M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002427

Adverse Event Rates for Select Analgesics

Event	Ultram ¹ 50-100 mg q4-6h	OxyContin ²	OxyContin Osteoarthritis 20 mg q12h	ABT-594 ³ 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

¹ Chronic non-malignant pain, up to 30 days (label)

² "Clinical trials" (label)

³ M98-826 and M98-833 combined

N/A - Not Available

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ABT-594

Phase IIa Conclusions

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
 - SEC tolerated better than predicted by solution
 - 75 mcg BID (HGC) very well tolerated vs. other analgesics
 - Two Phase I studies (M99-076 and M99-120) showed:
 - 300 mcg BID HGC tolerated
 - Titration may improve tolerability
- Full analgesic potential should be defined with adequate dose ranging studies in Phase IIb

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Phase IIb

- Trials

- Neuropathic Pain (M99-114)
 - Ongoing
- Osteoarthritis Pain (M99-115)
 - Unfunded

- Doses

- 150, 225, 300 mcg BID

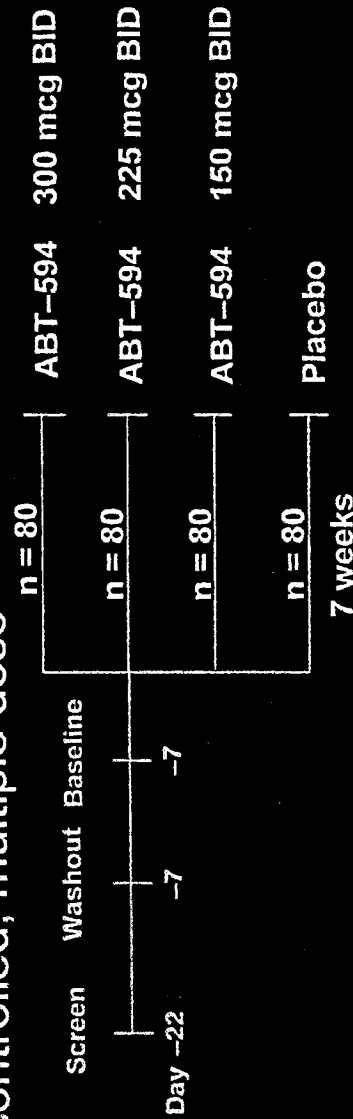
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M99-114: Neuropathic Pain

Design

- 320 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-Day primer phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)
- Hard Gelatin Capsule

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Collicott Deposition Exhibit 32

P's Exhibit EL

Part 4

M99-114: Neuropathic Pain

Outcome Measures

- **Primary**

- Weekly average of daily pain (11-point Likert in a diary)

- **Secondary**

- Site-based pain scale (11-point Likert)
- Neuropathic Pain Scale
- Patient Global Impression of Change
- Physician Global Impression of Change
- SF-36

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M99-114 Status

- Enrollment
 - Ended 1/5/01 at 269 subjects
 - Pre-specified power not reached
 - Width of confidence intervals not meaningfully different between 269 and 320 enrolled
- Database release – 5/01
- Go/No Go – 6/01

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ABT-594

Take Home Messages

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
 - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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**ABT-594 Project Review
February 2, 2001
Commercial Assessment**

**Andrea Landsberg
Laura Robinson**

**HIGHLY
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ABBT 0002436

ABT-594 Commercial Assessment: Key Take Aways

- Neuropathic pain market is the primary target
 - Underserved market with significant unmet need
 - ABT-594 has potential to be first novel drug in decades indicated for neuropathic pain
- Additional opportunity in “chronic persistent pain” market
- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*

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Neuropathic Pain Market: Sales

	2000 US Sales (\$MM)	2000 ex-US Sales
AEDs	\$299	\$190
TCAs	\$3	\$45
OPIOIDS	\$37	NA
OTHERS	\$85	\$45
TOTAL	\$424	\$280

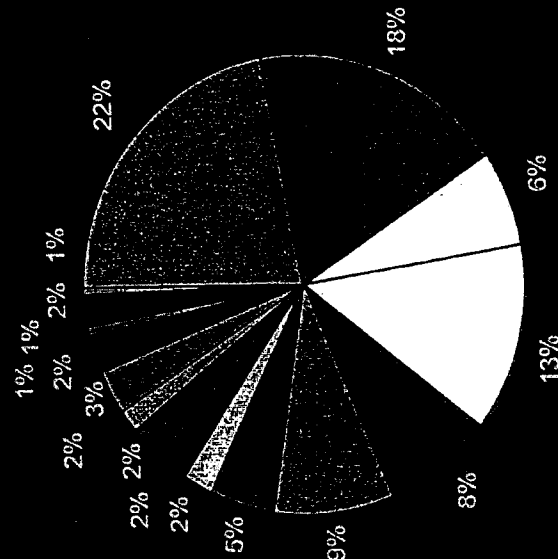
US Sales factored for neuropathic pain and annualized
Vs Prior Year: US Growth est 20%, ex-US growth est 10%

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Drug Classes Used to Treat Neuropathic Pain

*Dispersed market due to limited promotion
and lack of dominant effective product*



Drug Uses Data (not Rx or \$'s)

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Use in Neuropathic Pain

- Even if target only 'focused' indication in 'painful, diabetic neuropathy' expect trial and usage in all types of neuropathic pain
 - Neurontin use all off-label
 - Carbamazepine is indicated for trigeminal neuralgia but used in all neuropathic pain
 - Generally held premise that NP likely has some similar mechanisms across etiologies (reinforced by current drug usage)

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Market Opportunities in Neuropathic Pain

- Improved efficacy
 - Partial pain relief is the norm
 - Polypharmacy often required to manage pain
- Improved responder rates
 - Typically only 40% to 60% of patients respond to any given treatment
- Improved tolerability over time
 - TCAs, AEDs, opioids have troublesome SEs that do not diminish over time
- Dose reduction
 - Most TCAs and AEDs (including Neurontin) typically dosed TID
- Titration reduction
 - TCAs and AEDs require >2 weeks titration period to minimize SEs or reach effective dose

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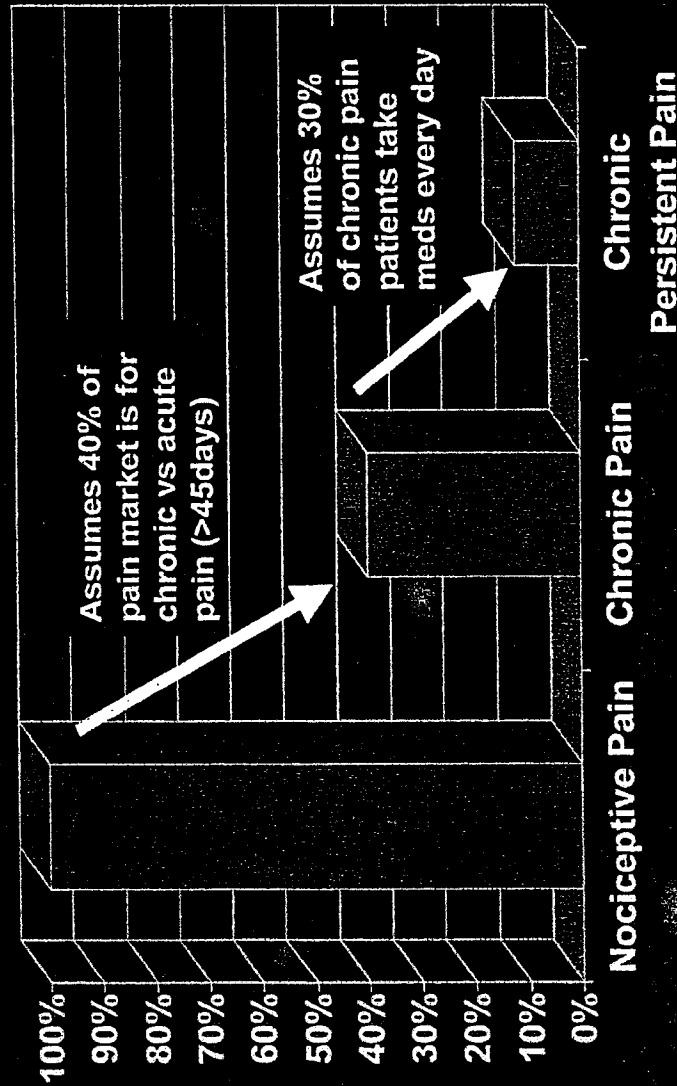
Chronic Persistent Pain (CPP) "Spillover"

- Onset of action and need for titration limits ABT-594 to a small segment of the nociceptive pain market
- CPP = Chronic persistent pain conditions for which patients are on daily medications, over extended periods of time (vs. PRN, or 'as needed', consumption)

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Chronic Persistent Pain



IMS Longitudinal Data indicates over 80% of pain meds Rxed for ≥ 30 days
Quantitative primary market research indicates that $>60\%$ of chronic pain patients take meds every day

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Chronic Persistent Pain Market

	1999 Sales (\$MM)	CAGR (97-99)	Rxs (MM)	CAGR (97-99)
US	\$700	5%	35	1%
Ex-US	\$680	8%	58	3%

CPP Market Size Assumptions:

Assume 40% of opioid, non-opioid, COX-2 market is for chronic pain and 30% of that is 'persistent', i.e.: medication taken every day

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Qualitative Market Research Results

Profile		Share of Patients		
Efficacy	AEs vs. current agents	OA	RA	Low-back

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

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Qualitative Market Research Results

Profile		Share of Patients		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent			
Same	Equivalent			
Better	Poor			

TCA's used as "benchmark" efficacy in NP

Tolerability vs. current agents: equivalent = 5% nausea; 5% vomiting; 10% dizziness; poor = 20% nausea; 10% vomiting; 30% dizziness

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ABBT 0002445

Qualitative Market Research Results

Profile		Share of Patients		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent	19%	12%	16%
Same	Equivalent	15%	8%	10%
Better	Poor	12%	6%	11%

Spillover market share in chronic persistent pain markets (in forecast, assuming only 5% share)

MR did not test impact of titration on market share

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Qualitative Market Research Results

Profile		Share of Patients
Efficacy	AEs vs. current agents	Neuropathic Pain
Better	Equivalent	31%
Better	Poor	24%
Same	Equivalent	27%

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

In forecast assuming 20% share of NP

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Neuropathic Pain Pipeline

- Pregabalin is in Phase III, but questions remain regarding Pfizer's Neurontin/Pregabalin strategy
- 4 NNR preclinical programs appear to be targeting pain indications; ABT-594 is much further along
- Other new AEDs may have potential for treatment of neuropathic pain and are conducting phase IV trials; unclear whether these agents will pursue an NP indication
- Several novel pain mechanisms being explored
 - Calcium channel blockers
 - Sodium channel blockers
 - NMDA antagonists

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Positioning of ABT-594 in Neuropathic Pain

- Greater efficacy than AEDs and TCAs in NP
- Better long term tolerability (than TCAs and opioids)
- Safe in all patient populations
- Convenient BID dosing with simple, short titration period
- No tolerance over time and non-scheduled
- Limited drug interactions
- Novel mechanism of action

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Positioning of ABT-594 in CPP

- Effective alternative to opioids with:
 - No tolerance, respiratory depression, constipation, etc.
 - Non-scheduled
- For patients receiving insufficient relief with current therapies or NSAID/opioid intolerant patients
- Better efficacy than COX-2s with novel mechanism of action and no major safety issues

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ABT-594 Global Forecast Ranges

(\$MM)

	Peak Sales		
	Low	Base	High
US	\$92	\$339	\$509
Ex-US	\$130	\$363	\$712

- NP shares: 5%, 20% or 30%
- CPP shares: 3%, 5%, 7%

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Key Product Challenges

- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*
 - Neurontin/Pregabalin may have advantage
 - Will need to minimize early DCs as much as possible
 - Potentially low therapeutic index
- *Titration*
 - Schedule must be as short and simple as possible
- *Nicotinic mechanism*
 - Will require pre-launch market education and priming to diffuse negative associations and generate interest surrounding novel MOA

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Go/No Go Process

Bruce McCarthy

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ABBT 0002463

ABT-594

Go/No Go Process

The Challenge

Integration of many interrelated data

Efficacy

Safety

Dose Response

Pharmacodynamics

Dose Selection

Phase III Trial Design

Titration Effects

Indications

Market Research

Segmentation

Targeting

Positioning

The Plan

Leverage decision analysis (DSG) as a process
to determine Go/No Go criteria

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ABBT 0002454

Collicott Deposition Exhibit 38

P's Exhibit FK

Franchisee		Dev Status		Brand Name		Generic Name		ABT-594		Neuronal Nicotinic Receptor Agent	
Neuroscience		Phase I		In progress		Ebanolone tosylate		2018		Treatment of pain associated with diabetic polyneuropathy	
<p>ABT-594 is a neuronal nicotinic receptor with potential efficacy in nociceptive and neuropathic pain</p>											
U.S. Market		Unit		Value		CAGR		<p>Unmet Need/Key Market Drivers</p> <p>US Significant unmet need in NP as many patients do not respond to currently available agents, many of which have unacceptable SEs. No branded marketed products currently indicated for NP (although Neurontin and/or gabapentin will likely be by time of launch). Chronic persistent pain population is growing with aging population and also has high unmet need for non-opioid options with high efficacy.</p>			
Sales		TRX		10.5MM		6%		<p>Key Competitors/Position to Market</p> <p>Neuropathic pain: Neurontin is taking strong lead in the market as increased MD awareness of efficacy coupled with ease of use becomes widespread, although it lacks an indication. Pregabalin is an alternative here made a first line in NP, although treatment patterns are diverse. Pregabalin is in development for NP also and may launch with indication before 594. Chronic pain (likely some spillover prescribing in this market for 594): COX 2s and opiates dominate this market, but additional options (from MOA) with better efficacy than NSAIDs, without the AEs and addiction potential of opiates are needed for chronic pain.</p>			
Sales		TRX		23MM		3%		<p>Neuropathic pain: Gabapentin (Neurontin) on market with limited commercial success at US (total 1999 sales 180 MM for usage in all indications). Carbamazepine is gold standard treatment, but is not indicated for neuropathic pain, and has undesirable side effects. Pregabalin currently in Phase III. ABT-594 expected to be first to market INN for neuropathic pain. Chronic pain (likely some spillover prescribing in this market for 594): Opiates reserved for only the most severe pain (e.g., cancer, post-op), thus large unmet need exists for non-scheduled, non-addictive agents for treatment of chronic pain.</p>			
Sales		TRX		140MM		8%		<p>Chronic pain: Agents with greater efficacy than currently available agents with adequate tolerability for chronic usage needed. Only one agent currently indicated for neuropathic pain (gabapentin - Neurontin).</p>			
Development		Cost to NDA		DOC		Est.		<p>Development Timeline</p> <p>Start of Test Phase I Phase II Phase III</p> <p>US, EU, Japan Approval</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
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Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cincals		\$0.0		\$0.0		<p>Actual</p> <p>10 1997</p> <p>30 1997</p> <p>30 1998</p>			
Development		Cincals		\$0.0		\$0.0		<p>DOC</p> <p>Q1 2002</p> <p>903, 903,504</p> <p>904,904,505</p>			
Development		Cinc									

April 2001

ABT-594

Monthly Highlights -- Key Project Progress

- Blind Broken on April 20 for M99-114 Painful Diabetic Neuropathy Phase II b study

Next Quarter's Key Progress Markers

Key Progress Marker	Target Date
• Go / No Go target for program	06/30.
•	
•	

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact Cost Time Profile Regulatory	Strategy/Progress	Area / Responsibility	Resolution Date Planned / Actual In-Process
Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.		PARD Analytical has completed their analysis of the lab-scale batch made with the Mitsunobu chemistry change in step 4. No issues have been identified. Additional evaluation continues, looking at samples from the in-process chemistry stages to see if there are any additional targets to look for. Some degradation studies have been started, with final characterization and / or isolation to be completed.	PARD Analytical	
		The first production-scale lot of drug substance manufactured using the Mitsunobu chemistry change in step 4 has been completed. The specifications were issued 4/24 (document DTP-RD0838.) Release testing will be initiated in May, and should be completed within the month. The lot will also be put on stability in May.	SPD / PARD Analytical	Release testing complete: May QA release: TBD

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April 2001

ABT-594

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact _ Cost _ Time _ Profile _ X Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study		<p>This issue has been reviewed with PARF, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made.</p> <ul style="list-style-type: none"> Progress continues on SPD's effort to synthesize 2 grams of purified F' material for further testing. PARF Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot. When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics. 	<p>SPD</p> <p>PARF Analytical</p> <p>Toxicology / Exploratory Kinetics</p>	<p>June-01</p> <p>TBD</p> <p>TBD</p>
	_ Cost _ Time _ Profile _ Regulatory			

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April 2001

ABT-594

Key Activities

Commercial		LBE	Actual
Activity			
Quantitative conjoin analysis regarding commercial viability of various efficacy/AE profiles and associated market share tradeoffs		6/01	
Qualitative market research regarding attractiveness of transdermal patch for severe pain or neuropathic pain patients		6/01	
NNR communication strategy		12/01	
ABT-594 publication plan		12/01	
Brand name registration submission (generic name approved 11/00 - ebanciline tosylate)		12/01	

Formulation		Plan	Actual
Activity			
Phase I Formulation (PIB)*		7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction		7/1998	7/1998
Phase II Formulation (SEC) for IND		7/1998	7/1998
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)		10/1998	10/1998
Phase IIB / Formulation (HGC) for Bio Study		3/1999	3/1999
Phase III Clinical Supplies Manufactured		9/2001	TBD
NDA Lots (3) Completed		5/2002	TBD
Completion of 1 Year Stability for NDA		7/2003	TBD
Formulation Peer Review		TBD	TBD

* Performed by IDC

Drug Substance		Plan	Actual	Actual / Projected Cost/kg*
Activity	KG			
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
ChemSyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
ChemSyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
ChemSyn NDA Lot #1 (Mesylate)	4.85 KG	10/1999	2/2001 **	\$ 29,700
ChemSyn NDA Lot #2 (Mesylate)	4.80 KG	10/1999	2/2001 **	\$ 29,700
ChemSyn NDA Lot #3 (Mesylate)	5.45 KG	10/1999	2/2001 **	\$ 29,700
ChemSyn Misunobu Lot#1	5.0 KG	04/2001		
ChemSyn Misunobu Lot#2	5.0 KG			
ChemSyn Misunobu Lot#3	5.0 KG			

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

** Bulk manufactured 1/2000, but delivery delayed due to Mesylate testing & QA release

Toxicology		Actual Start Date	Report Completed
Activity	Planned Start		
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	--	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing *
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing *

* In-life phase complete, and analysis / assessment in process

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April 2001**ABT-594****All Clinical Studies:**

Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients		Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients	
					Target	Current						Target	Current
M99-114	II	Safety & Efficacy vs placebo in Painful Diabetic Neuropathy	04/00	04/01	320	269 Final							

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April 2001

ABT-594

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Status: Enrollment Complete – 269 patients randomized

Major Findings: TBD

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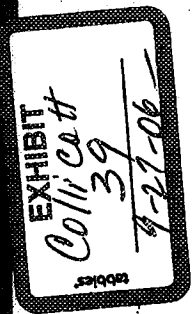
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Collicott Deposition Exhibit 39

D's Exhibit GN

W99-114 Study Review

4/23/01



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ABBT 0001749

M99-114 Neuropathic Pain

Study Results

- Summary
- Study design
- Efficacy results
- Adverse events
- Conclusions and next steps

4/23/01 PRELIMINARY DATA

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ABBT 0001750

M99-114 Neuropathic Pain

Summary

- Efficacy
 - 150, 225 and 300 mcg BID are significantly better than placebo
 - All three doses may have similar efficacy
- Safety
 - 150 mcg BID
 - Nausea: 34%
 - Vomiting: 15%
 - Dizziness: 17%
 - Abnormal Dreams: 22%
 - Dose dependent increase in adverse events
- Conclusion
 - ABT-594 significantly reduces diabetic neuropathic pain

4/23/01 PRELIMINARY DATA

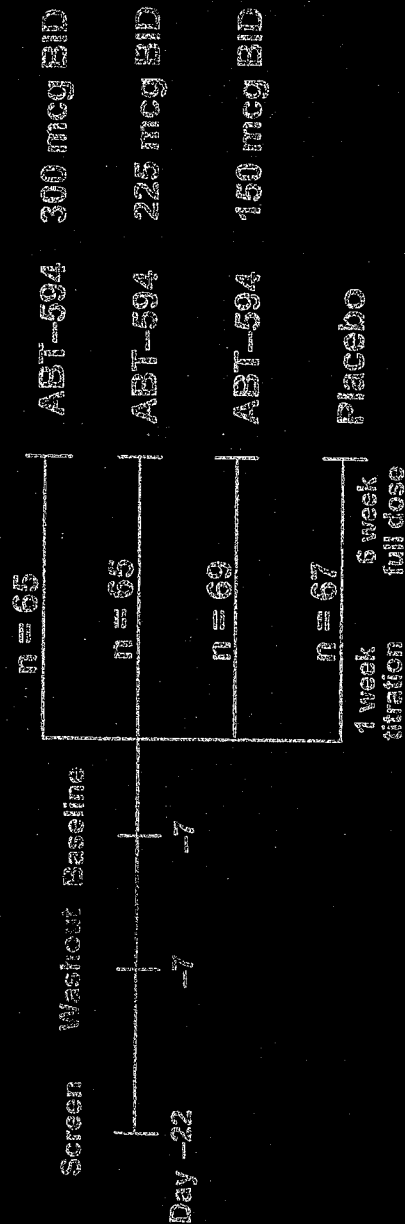
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ABBT 0001751

W199-114: Neuropathic Pain

Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I PRELIMINARY
- Concomitant analgesics disallowed

4/23/01 PRELIMINARY DATA

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ABBT 0001752

M99-114: Neuropathic Pain

Outcome Measures

- Primary
 - Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
 - Change from baseline to last 7 days on drug
- Secondary
 - Site-based Pain Rating Scale (11-point Likert)
 - Neuropathic Pain Scale
 - Patient Global Impression of Change
 - Clinician Global Impression of Change
 - SF-36

4/23/01 PRELIMINARY DATA

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ABBT 0001753

M99-114: Neuropathic Pain

Outcome Measures

• Pain Rating Scale

0	1	2	3	4	5	6	7	8	9	10
no pain										worst
										pain possible

• Neuropathic Pain Scale (NPS)

- 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp

1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	----

The most sharp
sensation
imaginable (like a
knife")

• Subject, Clinician Impression of Change

1	2	3	4	5	6	7
Much Improved	Moderately Improved	Minimally Improved	No Change	Minimally Worse	Moderately Worse	Much Worse

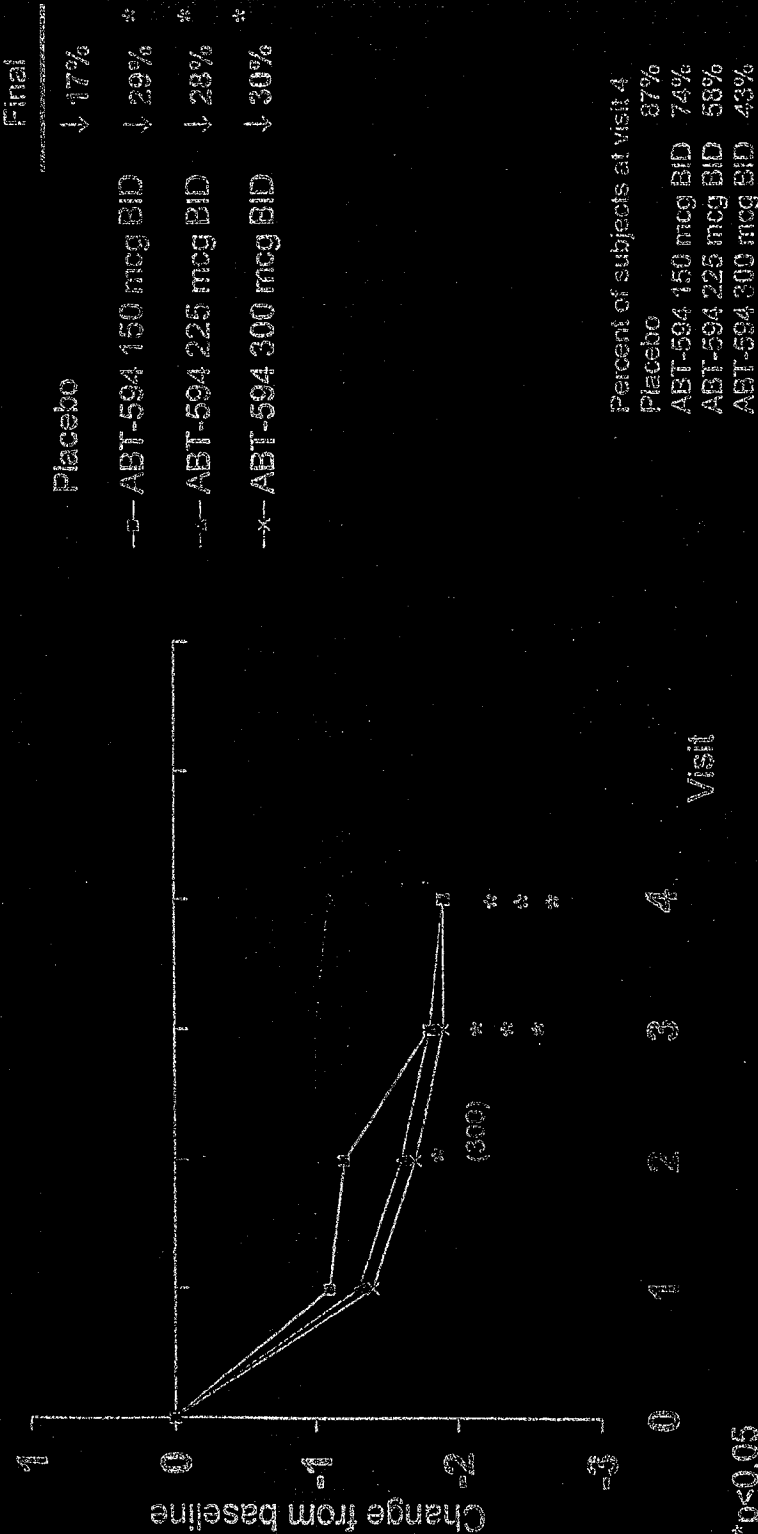
4/23/01 PRELIMINARY DATA

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ABBT 0001754

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Primary Efficacy Variable in the Intent to Treat Population

Pain Rating Scale-Diary (Between Visit Average) ^{Change: Baseline to Final}



4/23/01 PRELIMINARY DATA

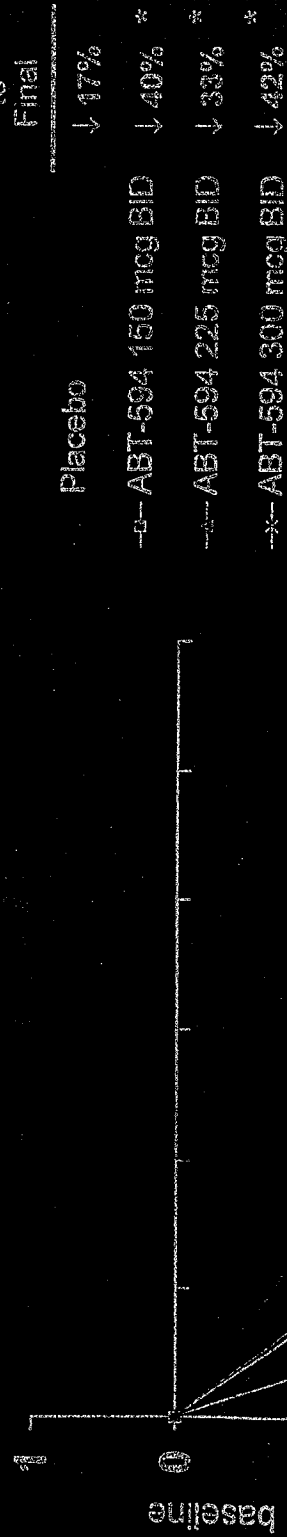
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ABBT 0001765

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale in the Intent to Treat Population

Pain Rating Scale (Site Based)

Change:
Baseline
to
Final



Percent of subjects at visit 4
Placebo 87%
ABT-594 150 mcg BID 74%
ABT-594 225 mcg BID 58%
ABT-594 300 mcg BID 43%

*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.7

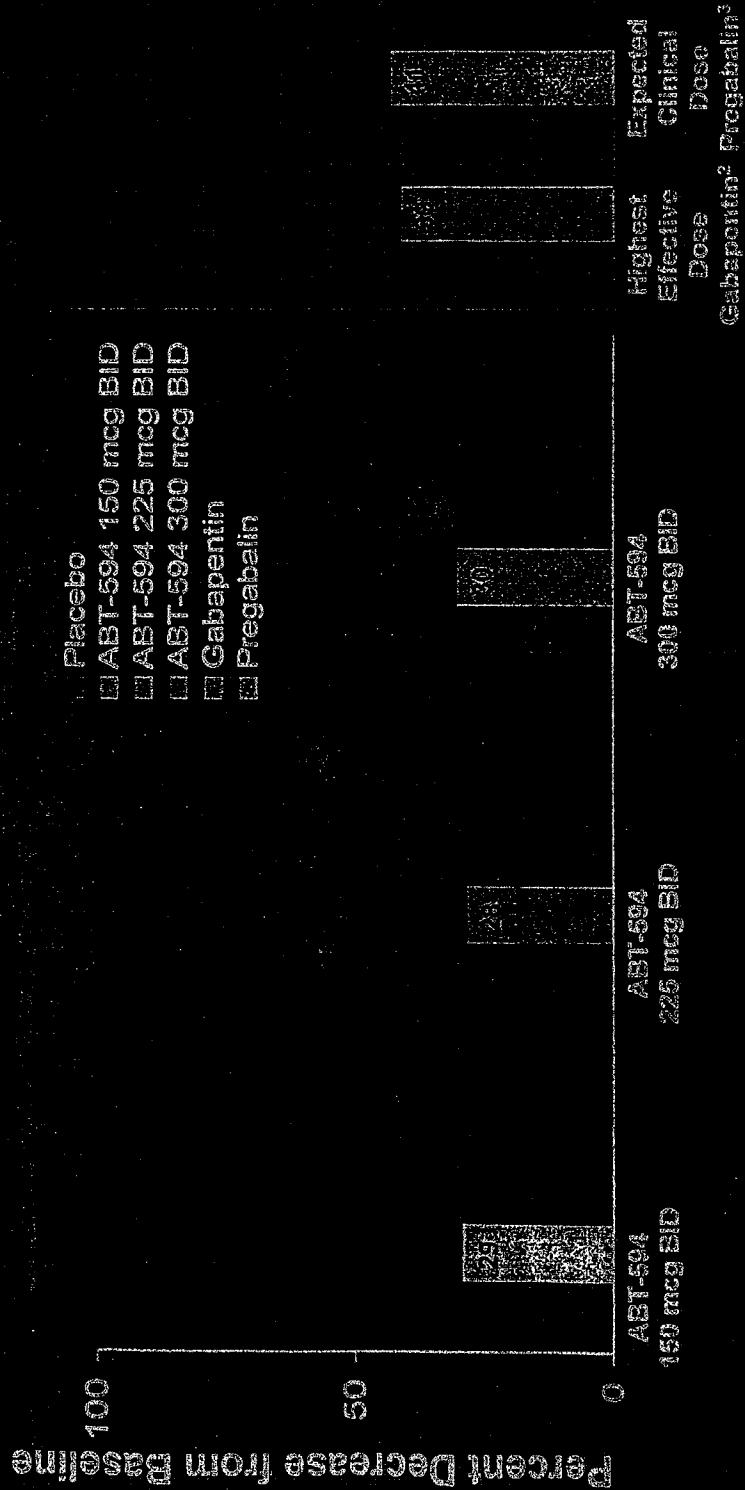
4/23/01 PRELIMINARY DATA

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ABBOT 0001766

ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain as Greatly as Gabapentin or Pregabalin (ITT)

ABT-594 vs. Gabapentin and Pregabalin



¹ 11-point Likert scale week 7 vs. baseline
² 11-point Likert scale week 8 vs. baseline
³ 11-point Likert scale week 5 vs. baseline

4/23/01 PRELIMINARY DATA

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ABBT 0001757

ABT-594 150, 225 and 300 mcg BID Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness

*Adverse Events**

Event	ABT-594		ABT-594	
	Placebo N = 65	150 mcg BID N = 65	225 mcg BID N = 69	300 mcg BID N = 67
Nausea	11 %	34 %	43 %	46 %
Abnormal Dreams	0 %	22 %	22 %	18 %
Headache	12 %	20 %	14 %	19 %
Dizziness	5 %	17 %	35 %	28 %
Vomiting	3 %	15 %	25 %	21 %
Diarrhea	3 %	11 %	12 %	6 %
Dyspepsia	3 %	8 %	12 %	7 %
Asthenia	2 %	6 %	16 %	19 %

*Occurring in ≥5% 150 mcg BID ABT-594 treated patients and ABT-594 incidence > placebo.

4/23/01 PRELIMINARY DATA

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ABBT 0001768

Collicott Deposition Exhibit 42

P's Exhibit FV



Judith S
Brownell/LAKE/PPRD/ABBO
TT

06/18/2001 02:15 PM

Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT, Joan M
Freehoff/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, James W
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Karen L
Cox/LAKE/PPRD/ABBOTT@ABBOTT, Beth H
Wilson/LAKE/PPRD/ABBOTT@ABBOTT, Katherine M
To Landwer/LAKE/PPRD/ABBOTT@ABBOTT, Jeffrey L
Kahn/LAKE/PPRD/ABBOTT@ABBOTT, Alyssa B
O'Neil/LAKE/PPRD/ABBOTT@ABBOTT, Rich
Manski/LAKE/PPRD/ABBOTT@ABBOTT, Marian L
Borgstrom/LAKE/PPRD/ABBOTT@ABBOTT, Judy A
Anderson/LAKE/PPRD/ABBOTT@ABBOTT, Nancy
Hollis/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject RELEASE OF DATABASE, M99-114 (MC114A), ABT-594

The Data Management process has been completed for study M99-114 (ABT-594) and the database, MC114A was transferred to statistics for analysis on 18/Jun/01 at 15:07. Any subsequent changes to this database will be captured via audit.

LAST CASE REPORT FORM RECEIVED:	15/Mar/01
LAST DATA RECEIVED:	15/Jun/01
NUMBER OF PATIENTS IN DATABASE:	266

Assays have not been loaded

Status of the QA process:

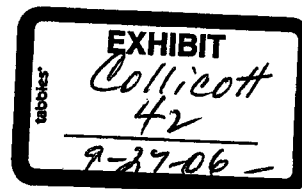
UNADDRESSED QUERIES:	0
OUTSTANDING ADDENDA:	0
OUTSTANDING ISSUES:	This database is being released with xeroxed addenda (originals pending signature by the site). Assay analysis results to be received at a later date and loaded

Access to the MC114A database will be limited to Katie Landwer and Judy Brownell. Please contact us with any issues regarding this database.

Thank you.

jb

Confidential



ABBT239029

Collicott Deposition Exhibit 45

P's Exhibit GH



Marilyn J
Collicott/LAKE/PPRD/ABBO
TT
10/05/2001 12:16 PM

To: JanLips710@aol.com

cc:

bcc:

Subject: Re: (no subject) []

Yeah - I love the ken and Judy stories, too, and they just keep getting better and better

My Mom hasn't asked him yet - she will this weekend at the wedding. And, yes, he is retired - been so for more than a year now. (And you'd have never known it when my Dad was sick and in the nursing home.....).

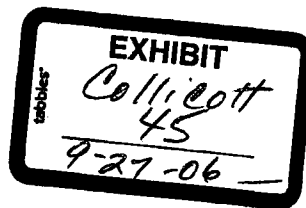
ABT-594 is on life support but they haven't pulled the plug yet - we may be doing a titration study - soon! ABT-089 (ADHD) FTIM is set to begin dosing in early November. I'm going to Germany to do an initiation visit during the week of 22 OCT. ABT-963 (COX II) is still rolling around poking it's head up now and then - no official start yet. Hey - how'd you like that big TAP settlement for Lupron - yikes!

I will keep you posted on all the fun, new, developing events that occur this weekend in Onalaska

m

p.s. Jane and I were supposed to be in Alaska this week but decided to cancel because the airline schedules were all screwed up. Our connections in and out of Anchorage had been cancelled every day for the last 2 weeks - not a good sign. We will go again in February for Fur Rondy - wahoo!

Highly Confidential



ABBT241303